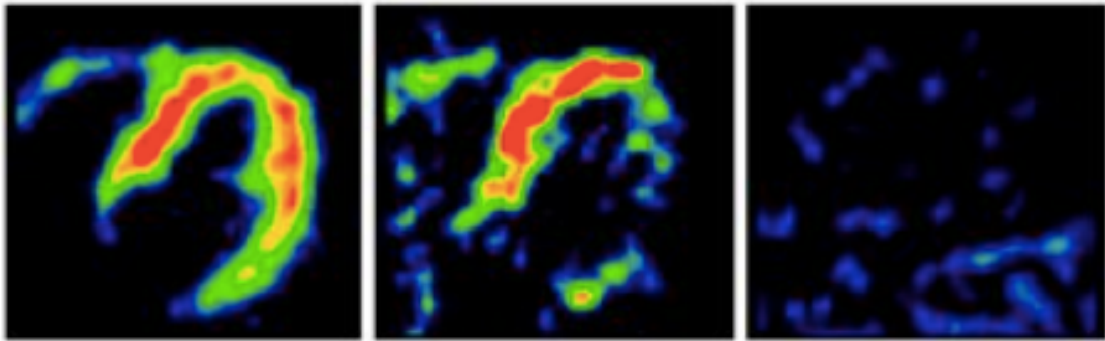


Principles of Autonomic Medicine



David S. Goldstein, MD PhD

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DEDICATION

I dedicate this book to my family, for their support and understanding; my colleagues and friends at the NIH, for their devotion to our research mission and to me; and especially to the many patients who have put their trust in me and provided me with sparkles of insight about how the body's "automatic" systems function in health and disease.

I've benefitted from a rich network of NIH colleagues, whom I have cherished for their sharing time with me in a common quest for truth and meaning. Some of these, in alphabetical order, are: Ines Armando, John Bacher, Krys Bankiewicz, Oladi Benthó, Alan Breier, Richard Cannon, Peter Chang, Glen Cook, Adele Cooney, Abraham Corrales, Nadir Dakak, Raghu Dendi, Ray Dionne, Yu-Fe Duan, Graeme Eisenhofer, Basil Eldadah, Igor Elman, Giora Feuerstein, John Finberg, Joan Folio, Steve Frank, Koki Fukuhara, Moshe Garty, John Gill, Anna Golczynska, Phil Gold, Ehud Grossman, Aaron Hoffman, Courtney Holmes, Thanh Huynh, Richard Imrich, Risa Isonaka, Yunden Jinsmaa, Steve Kaler, Harry Keiser, Joong-Seok Kim, Ken Kirk, Irv Kopin, Richard Kvetnansky, Ray Lake, Itzhak Lamensdorf, Jacques Lenders, Paul Levinson, Shengting Li, Roshanak Mansouri, Jeff Moak, Alex Neumeister, Karel Pacak, Miki Palkovits, Mee Yeong Park, Jigisha Patel, Sandra Pechnik, Ron Polinsky, Faisal Rachman, LaToya Sewell, Yoni Sharabi, Ellen Sidransky, Cathy Sims-O'Neil, John Stuhlmuller, Robin Stull, Patti Sullivan, Kate Szemerédi, Cees

Tack, Dnyanesh Tipre, Olga Tjurmina, Alex Vortmeyer, Efrat Wolfovitz, Gal Yadid, Reuven Zimlichman, and Zofia Zukowska.

Dr. Irwin J. (“Irv”) Kopin was my boss and mentor, and I honor his memory with this book. As Chief of the Laboratory of Clinical Science at the National Institute of Mental Health, then as Scientific Director of the National Institute of Neurological Disorders and Stroke, and then as Scientist Emeritus, he was an example of intellectual rigor, productivity, perspective, and integrity, an inspiration throughout my career at the NIH. Our style of interaction was to argue about the science. We would argue about interpretations of the data, about which experiments to do and how to do them, about conceptual models, about getting the historical facts straight. I think we were following the uniquely Jewish tradition of the *chevrusah*, the talmudic learning partner. Two people try to understand the material by discussing and debating it together. I feel thankful that Irv was my medical scientific *chevrusah* for so many years.



Irv Kopin and Courtney Holmes

Courtney Holmes ran our Section's catecholamine neurochemistry lab for 28 years. She retired recently but continues to contribute part-time as a contractor. I think of Courtney as the Cal Ripken of catechol assays. Cal played infield for baseball's Baltimore Orioles for 19 years. He was elected to baseball's Hall of Fame for his amazing consistency. He made it look easy, because of his attention to detail, work ethic, and monumental expertise. Courtney has the same qualities. She points unerringly to the truth. If there were a catecholamine Hall of Fame, Courtney surely would be in it.

Finally, I remember with awe and appreciation the patients who requested they be autopsied to enhance understanding of their disease—the ultimate act of philanthropy. They have been some of my greatest teachers. I feel honored and humbled and would name them here but for respect of privacy and confidentiality.

INTRODUCTION

The View from Building 10

I sit in an office/lab in Building 10, the Clinical Center of the National Institutes of Health—“the NIH”—in Bethesda, Maryland. The yellow arrow shows where I am. Building 10, with the Hatfield Clinical Research Center added in front of it, is the largest research hospital on earth.



Building 10, the NIH Clinical Center, in Bethesda, MD.

Titans of academic medicine have passed through Building 10 during their training. I came here fresh from internal medicine residency in 1978. I’ve been here ever since.

I’ve been in Building 10 so long, it occupies me. In this book I’ll be presenting autonomic medicine from the viewpoint of a

dyed-in-the-wool clinical researcher.

In Building 10 I've been privileged to develop several clinical autonomic tests and apply them for the first time—especially in patients with uncommon or unique conditions. The combination of new technology and patients with rare diseases sets the stage for discoveries and based on those discoveries insights that induce new concepts.

In this respect I feel like I am following a tradition that goes back to William Harvey, the father of modern medical research. In 1657 he wrote, “Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by the careful investigation of cases of rarer forms of disease. For it has been found in almost all things, that what they contain of use or of application, is hardly perceived unless we are deprived of them, or they become deranged in some way.”

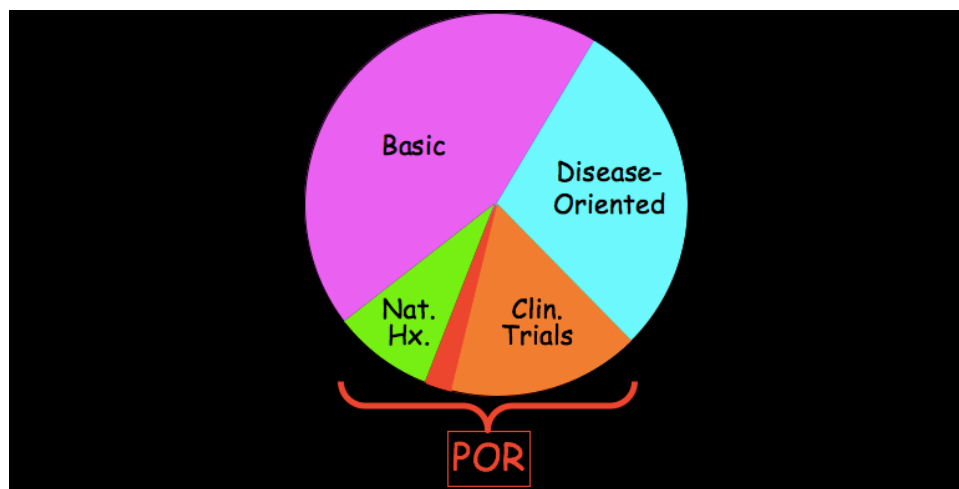
I hope to share the excitement that comes from making medical scientific discoveries and to convey the historical, cultural, and societal significance of an extraordinary field of knowledge—the autonomic nervous system.

Patients as a Scientific Resource

The type of research I do is called patient-oriented research. You're doing patient-oriented research if you shake hands with the subject matter.

Patient-oriented research is rare. Most biomedical research is basic. The focus is on a particular cellular process or molecule or technology without regard to a disease. In disease-oriented research, the goal is to understand diseases, such as via animal models, genetic material from patients, or population studies.

Within the domain of patient-oriented research, most of the activity is in designing, conducting, and reporting results of clinical trials of new treatments or in studying the natural history of diseases—what happens to the patients over time with standard treatments. Patient-oriented research with the goal of understanding mechanisms of disease is a rarity within a rarity.



Patient-oriented research is unusual. Patient-oriented research to understand disease mechanisms (the red sliver) is rare.

Nevertheless, patients provide a tremendous scientific resource, for the obvious but important reason that only patients can tell you what and how they feel. It's the job of patient-oriented researchers to learn what their patients teach.

Why Did I Write this Book?

First, I wrote this book to teach trainees in autonomic disorders. The fellowship in autonomic disorders at the NIH is accredited by the United Council for Neurological Subspecialties (UCNS). I want to help autonomics fellows pass the UCNS certifying examination.

Second, this book conveys an integrative approach to autonomic medicine. The founding concepts of cybernetic medicine, such as negative feedback regulation and homeostasis, are relatively simple to grasp and straightforward but nevertheless profound and powerful for understanding clinical autonomic disorders. Dysautonomias provide a platform for linking systems biology with integrative pathophysiology.

Third, I wrote this book to highlight clinical catecholamine neurochemistry and neuroimaging. These are extremely informative but underutilized ways to diagnose and understand the pathophysiologic mechanisms underlying many autonomic disorders. At this point you may not even know how to pronounce the word, “catecholamine,” much less appreciate the medical, scientific, and even cultural significance of the three simple chemicals that make up the catecholamine family. Other autonomics textbooks do not go into these matters in depth. I’ve been entranced with catecholamines for most of my life. I hope reading this book will turn you into a catechol-aholic like me.

Fourth, I’ve designed this book to be a resource that patients,

students, clinicians, and academicians can share. This is a tall order because of the obvious differences in education, competencies, vocabulary, needs, and expectations across these readerships. I hope this book will help empower and give responsibility to patients—i.e., “flip the clinic.”

What is Different about this Book?

This book is a monograph, surely a rarity in modern academic medicine. A single-authored medical textbook has inherent advantages and disadvantages. An advantage is consistency in the presentation. Over the years I’ve developed a particular approach to clinical evaluations and research and a style of teaching about autonomic and catecholamine-related disorders. Students may acquire the material better if it is presented consistently across chapters.

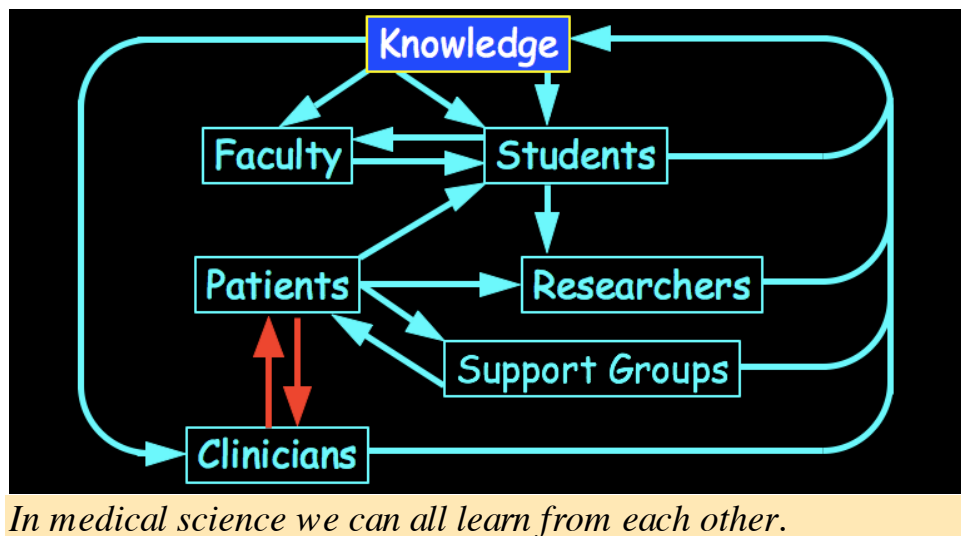
There are also disadvantages of having a single author. This is a highly personal account. The presentation is eclectic rather than encyclopedic. Many topics are covered cursorily, and some potentially relevant topics aren’t covered at all.

The discipline of autonomic medicine is immense. No one has sufficiently comprehensive knowledge of the subject matter. Like everyone else, I think that what I see is all there is, and I over-emphasize what I’ve observed or published. I’ve included some viewpoints for which the supporting data are incomplete or admittedly non-existent, to pique interest. I try to point out when I’ve done this.

THREE A'S OF STICKY TEACHING

In writing this book I've used three ways to make the teaching points "sticky." By "sticky" I mean memorable. The points stick in your head. For stickiness I've depended on art, analogy, and anecdote.

I've exploited a talent for drawing and cartooning to convey concepts that would be difficult to grasp from the text alone. Many figures in this book are concept diagrams. I use the figure legends to convey the key teaching points as text.



For instance, in the figure above, the arrows show the reciprocal influences and feedback loops among stakeholders in autonomic medicine. Clinicians instruct patients, but patients also teach clinicians. Support groups advocate for earmarked research funding and enable patients to be in contact with each other. Faculty learn from students about how to teach as much as students learn from faculty. Each group enhances

knowledge, which in turn informs all the others—along the lines of Edward O. Wilson’s “consilience” idea. Consilience refers to a convergence of evidence from independent, unrelated sources that enables strong conclusions. The



Edward O. Wilson, the author of “Consilience: The Unity of Knowledge” (from the announcement of Wilson’s NIH Director’s Lecture in 2002 in Building 10)

underlying principle is the unity of knowledge.

It’s not easy balancing scientific correctness vs. stickiness. Concept diagrams, analogies, and anecdotes can be incomplete, overly simplistic, biased, or just plain wrong.

Eternal vigilance is the price of “stickiness.”

I’ve also tried to spice up the book with sprinkles of wit. This

sort of whimsy may not be to everyone's taste. Topic headings in this book include "A Little Pain Can't Hurt" and "A Waist is a Terrible Thing to Mind." At times (like now) I'll be pointing out that what you just read was funny. My sense of humor has been described as "wry" and my writing style, well, "interesting."

A SHARED RESOURCE

Because of the different readerships, writing this book has posed several challenges, which I've tried to meet as follows.

The text highlighted in blue is taken in large measure from my book, *Dysautonomias: A Handbook for Patients*. Hopefully, lay people, patients, and caregivers will be able to comprehend the highlighted text. At the end of the book is a large glossary. Hovering over words or phrases pops up balloons that show the definitions in the glossary.

The text highlighted in blue is for lay people and patients.

To help students and trainees grasp the scientific concepts, I've drawn many figures and diagrams. The figure legends in italics provide a kind of parallel text.

For clinicians there are descriptions of several autonomic function tests, emphasizing, however, that the most informative test is an intelligently obtained medical history. I've also included concepts underlying several treatments, recognizing that management of autonomic disorders should be tailored to

the individual condition and patient; that reassurance, accurate information, and empathy often are at least as effective as drugs; and that education is itself an effective treatment.

For academicians I'm proposing a few ideas that seem to me to have potential for enhancing understanding of autonomic and catecholamine-related disorders. Some of these ideas are homeostats as metaphors, allostatic load, catecholamine autotoxicity, and cybernetic medicine. I decided against incorporating literature citations, however, because I don't consider this book to be more of a teaching aid than a rigorous academic treatise.

I hope this shared resource is be a first step toward “flipping” both the classroom and the clinic in autonomic medicine, by giving students more power and responsibility in their education and by giving patients more power and responsibility in their clinical management.

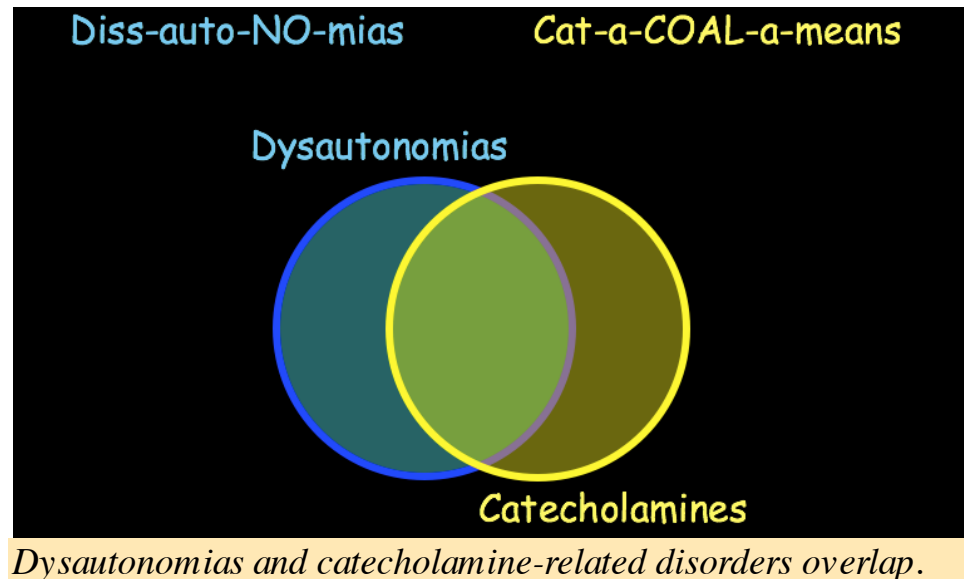
Diss-auto-NO-mias and Cat-a-COLA-means

This book is founded on two pillars—dysautonomias and catecholamines.

The reason for the overlap between dysautonomias and catecholamines is that key parts of the automatic nervous system use catecholamines as their chemical messengers.

Dysautonomias are a particular class of medical disorders. Catecholamines are body chemicals that often are related to those disorders. Unfortunately, both the disorders and the chemicals have names that are hard to pronounce. The disorders are dysautonomias, pronounced diss-auto-NO-mias. The chemicals are catecholamines, pronounced cat-a-COAL-a-means.

By measuring levels of the messengers, we can learn about how those parts work in health and disease. From identifying specific abnormalities or vulnerabilities of catecholamine-related systems, we can understand the mechanisms and might even come up with new therapeutic or preventive strategies for particular disorders.



We'll be getting to catecholamines later on, but for now, by way of introduction, the catecholamine chemical family has

only three members —dopamine, norepinephrine, and epinephrine (synonymous with adrenaline). All are vitally important, but in different ways.

There are a large number of conditions in which altered functions of one or more components of the autonomic nervous system adversely affect health. As a group they are called dysautonomias.

The most famous catecholamine is adrenaline.

Why are Dysautonomias So Hard?

Dysautonomias are a difficult subject, for patients, doctors, students, and researchers. Dysautonomias are hard to live with, diagnose and treat, and understand.

There are several reasons for this. I think it's important to explain at the outset why the field of dysautonomias is so hard.

DYSAUTONOMIAS ARE MULTI-DISCIPLINARY

The field of dysautonomias spans multiple disciplines of medicine. Specialists within these disciplines often cannot serve dysautonomia patients.

If your only tool is a hammer, the world looks like a nail. If a dysautonomia patient sees a cardiologist, the cardiologist looks for an abnormal heart rhythm or heart block, something a pacemaker or ablative therapy can treat. If the patient sees a neurologist, the neurologist looks for a seizure disorder, a problem with blood flow to the brain, a brain structural abnormality, or a neuropathy. If the patient sees an endocrinologist, the endocrinologist looks for diabetes or a thyroid, adrenal, or pituitary problem. If the patient sees an immunologist, the immunologist looks for autoimmunity or mast cell activation. If the patient sees a gastroenterologist, the gastroenterologist looks for gastro-esophageal reflux, decreased gut motility, or irritable bowel syndrome. If as often happens the patient finally sees a psychiatrist, the psychiatrist looks for depression, anxiety, a “conversion reaction,” or panic disorder.

Cardiology (heart rhythm & rate problems, heart failure, hypertension)
Neurology (seizures, Parkinson's disease, Chiari malformation, neuropathy)
Endocrinology (diabetes, thyroid problems, adrenal problems)
Gastroenterology (esophageal problems, irritable bowel, constipation)
Psychiatry (depression, anxiety, conversion reaction)
Pediatrics (fainting, inherited/congenital disease, POTS)
Pain Medicine (migraine, fibromyalgia, neuropathic pain, TMJ disorder)
Immunology (Sjogren's, auto-immune disorders, mastocytosis)

Several medical disciplines involve dysautonomias. Here are some examples.

DYSAUTONOMIAS ARE INTEGRATIVE

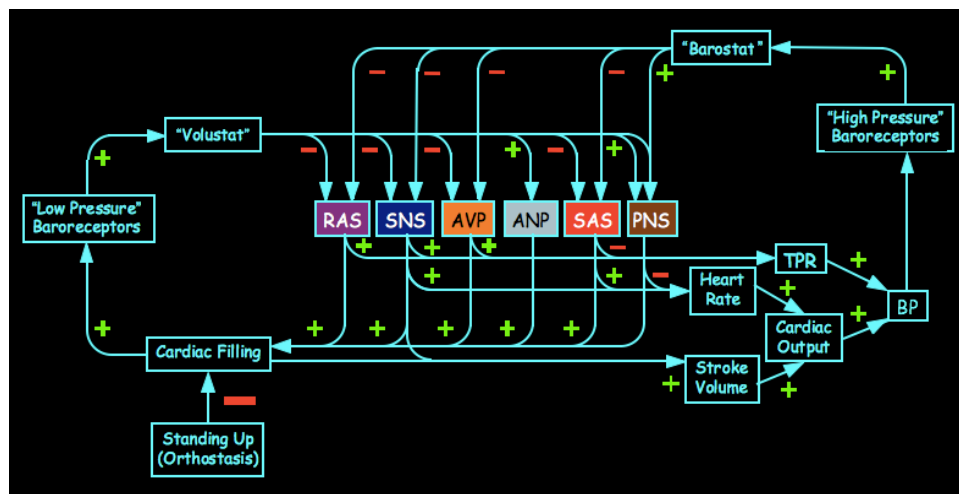
Many factors determine levels of pulse rate, blood pressure, body metabolism, pain, fatigue, and the sense of psychological well-being. These factors interact complexly with each other.

Further complicating the picture, patients with dysautonomias often are treated with multiple drugs, which not only can interact with each other but also with the disorders. Scientific theories taking this complexity into account have lagged behind.

Diagrams depicting disorders of feedback regulated systems can appear dauntingly complex. At their core, though, as you will learn, they all involve abnormal functioning of negative feedback loops.

This book teaches that dysautonomias are usually if not always disorders of integration, of regulation, of systems that change during life as a function of the balance of wear and tear vs. resilience.

Partly because of the multi-disciplinary nature of dysautonomias, peer-review committees tend to view grant applications about dysautonomias as somewhat foreign or of secondary importance. The NIH is a major source of funding in American biomedicine, and clinical disorders of the autonomic nervous system don't fit well under the umbrella of any NIH Institute. Considering the public health burden posed by



Dysautonomias are integrative medical disorders. They involve many complex networks, effector systems, and feedback loops.

dysautonomias, research funding in an attempt to reduce that burden is remarkably scarce.

DYSAUTONOMIAS ARE MIND-BODY DISORDERS

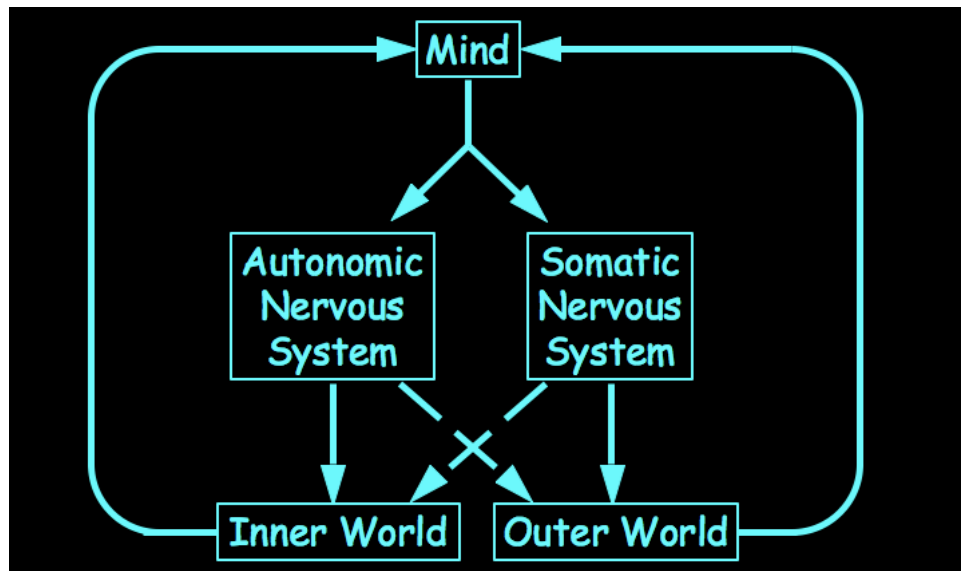
Are dysautonomias in the mind or body? The answer is: both.

Dysautonomias are “mind-body” disorders, which goes against a distinction between mental and physical body processes.

A major purpose of this book is to teach that the many symptoms of dysautonomias reflect real biological or chemical changes. If a clinician cannot identify the cause of a patient’s symptoms, this ignorance should not lead to dismissing the

patient as having a psychiatric rather than a “real” problem.

It is unhelpful to classify dysautonomias—or the patients suffering with them—as “psychiatric” or “medical.”



Dysautonomias are mind-body disorders.

Medical tradition separates mental from physical illness. Distinctions between the “body” and the “mind,” between the physical and the mental, and between problems imposed on the individual as opposed to those originating in the mind of the individual, are unhelpful in trying to understand dysautonomias, because the autonomic nervous system operates exactly at the ineffable border of the mind and body. In this book you will learn a systems approach to the mind-body issue.

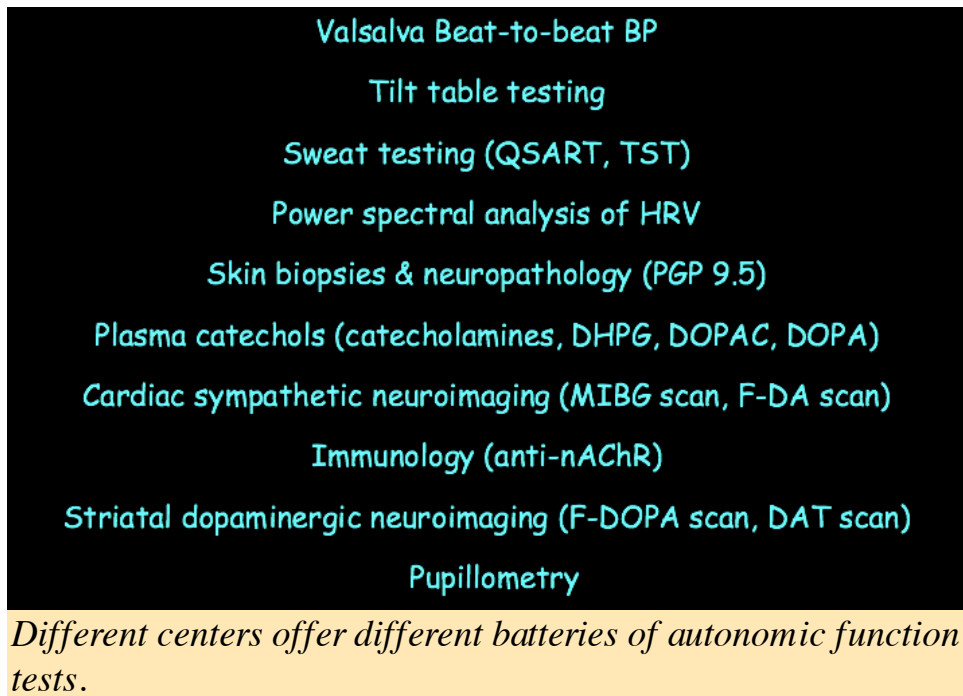
DIFFERENT CENTERS HAVE DIFFERENT EMPHASES

In almost every aspect of autonomic medical practice and research, doctors—even experts in the field—can disagree about answers to key questions. How should dysautonomias be classified? What are the types and subtypes? Of what do patients with particular dysautonomias complain? Which tests are useful to diagnose particular dysautonomias or monitor responses to treatments? What are the disease mechanisms? Which treatments work for which forms of dysautonomia? What happens to patients with dysautonomias over time?

Different centers have different emphases in the workup and management of dysautonomias. One center traditionally has focused on familial dysautonomia, a rare pediatric disease. Another has emphasized dysautonomia associated with diabetes, another disorders of sweating, another chronic orthostatic intolerance and multiple system atrophy, and another autoimmune autonomic ganglionopathy.

Different centers offer different tests, often depending on factors such as finances and insurance coverage. In my opinion these aspects have impeded the adoption and application of valuable, powerful clinical laboratory technologies.

No center outside the NIH has an integrated program of neuroimaging and neurochemistry. Tests that are done at the NIH for research purposes are not approved by the FDA as diagnostic tests; the tests often are not available at other centers because lack of insurance coverage.



DYSAUTONOMIAS ARE NOT TAUGHT WELL

I don't think the field of clinical disorders of the autonomic nervous system is taught well, at any educational level. Medical and graduate school curricula rarely contain coursework on dysautonomias. Compared to the large patient demand and public health burden, clinical and basic training and scientific knowledge about dysautonomias are disproportionately sparse.

The recent accreditation by the United Council for Neurologic Subspecialties (UCNS) of fellowships in autonomic disorders is a step in the right direction. As of this writing, however, there are only a handful of accredited fellowship programs in autonomic medicine.

Whether you are a lay person, a patient, a caregiver, a student, a general physician, or even a specialist in neurology, cardiology, endocrinology, or psychiatry, my guess is that the field of dysautonomias is almost completely foreign to you. Dysautonomias are not taught well, at any level of education.

I'd greatly appreciate your corrections, comments, and suggestions.

Please let me know if this book works for you, by sending me an email at goldsteind@ninds.nih.gov.

WHAT IS THE AUTONOMIC NERVOUS SYSTEM?

We all have a nervous system. What makes up this system? What do the parts of the nervous system do? And what is the “autonomic” part of the nervous system? This section is about your nervous system and how it functions when there is nothing wrong with it. You will need to understand the basics before you can understand the problems that can develop.

The autonomic nervous system is the body’s “automatic nervous system.”

To keep you alive and thrive, your body has to be able to coordinate many different activities. Some of these activities are voluntary and conscious, like moving your legs to walk across the room, while others are involuntary and unconscious, like breathing and digesting.

The autonomic nervous system is responsible for many of the automatic, usually unconscious processes that keep the body alive and stable, such as:

- controlling blood flows to the brain and other organs, both while you are at rest and while you are exercising
- keeping the right body temperature

- digesting food for energy production and fuel delivery
- getting rid of waste products in the urine and feces
- generating warning signs such as sweating, turning pale, and trembling in dangerous situations.

THE CNS IS LIKE A TOOTSIE ROLL POP

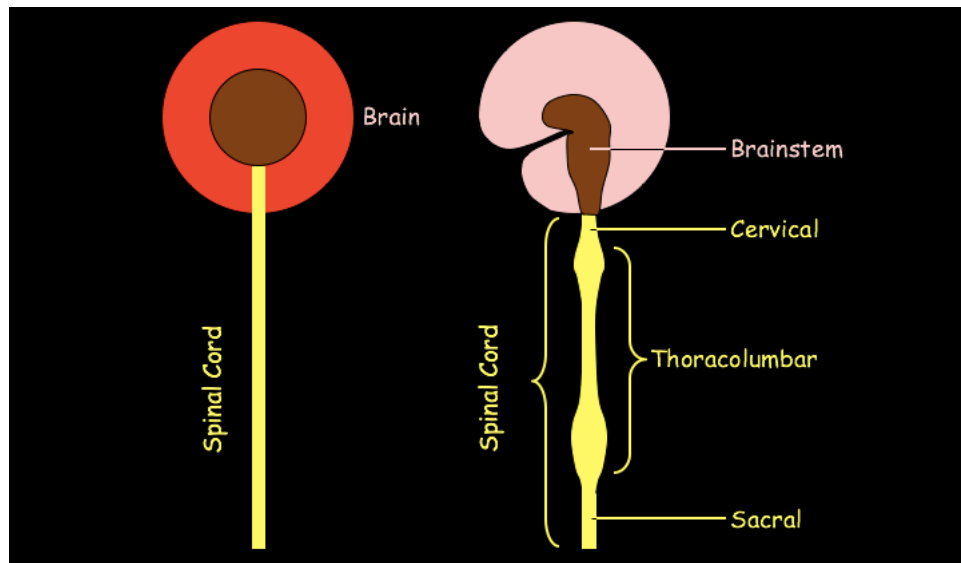
The central nervous system is made up of the brain and the spinal cord. The brain is like a command and control center. The spinal cord is a rope of nerves that runs from the base of your brain down through your back within your spinal column.



The central nervous system is like a Tootsie Roll Pop.

The central nervous system (CNS) is like a Tootsie Roll pop. The brain is the candy. The spinal cord is the stick. The chewy chocolate center is the brainstem.

The spinal cord is divided up into regions or levels. The cervical spinal cord is in the neck. Below this are the thoracic and lumbar spinal cord (the two parts together are the thoracolumbar spinal cord), and the lowest level is the sacral spinal cord. Autonomic nerves are derived from the brainstem



The brainstem is in the brain at the top of the spinal cord.

and the thoracolumbar and sacral spinal cord.

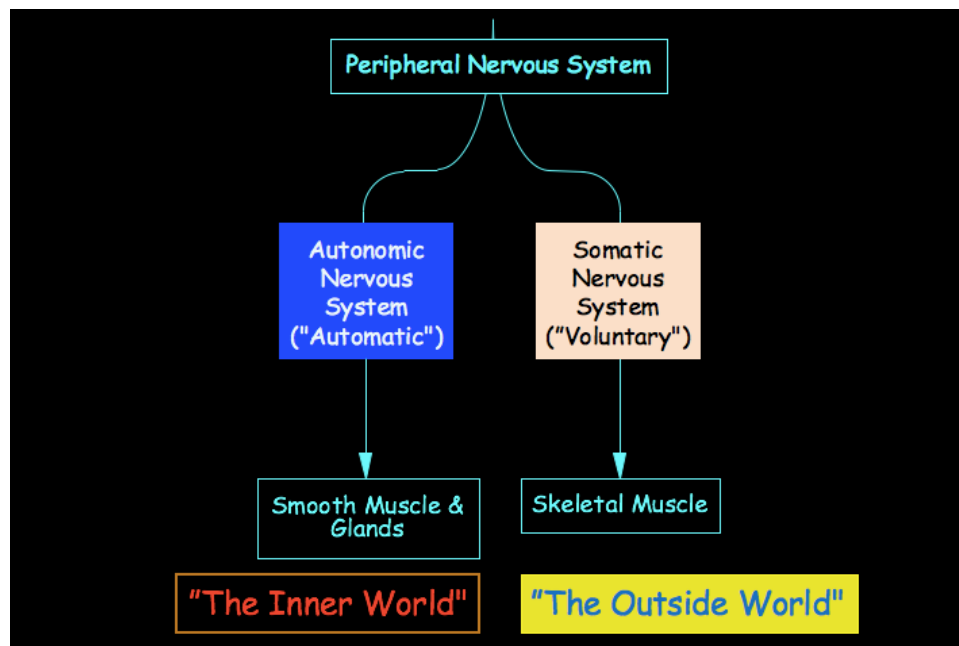
THE AUTONOMIC NERVOUS SYSTEM ISN'T AUTONOMIC

Control signals travel from your brain to your limbs and organs by way of the peripheral nervous system. The peripheral nerves are all the nerves that lie outside the brain and spinal cord.

Inside you is the “inner world” of your body, with its many internal variables, such as blood oxygen and glucose, blood pressure, and core temperature. Normally these variables don’t actually vary by much. They are kept in check. This is a key task in maintaining organismic integrity. The task is accomplished largely because of the component of the

peripheral nervous system that helps regulate the inner world—the autonomic nervous system.

The peripheral nervous system has two main divisions—somatic and autonomic. The somatic nervous system deals with the “outside world” of everything around us. It uses sense organs to detect what is going on outside, and it uses skeletal muscles to move.



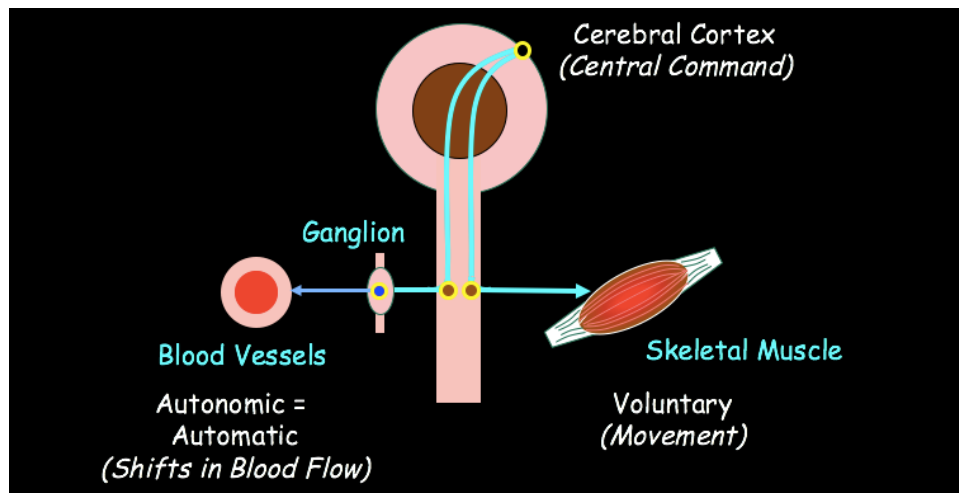
The peripheral nervous system consists of the autonomic nervous system and the somatic nervous system.

The autonomic nervous system is a key system by which the brain regulates the “inner world” inside the body. The autonomic nervous system really isn’t “autonomic,” but it is “automatic.”

In general, voluntary behaviors arising from the central nervous

system are linked to changes in organ function mediated by the autonomic nervous system. When you clench your fists, after several seconds your blood pressure increases. When you get out of a hot shower and walk into a cool locker room, you develop goose bumps. When you stand up from lying down, your blood vessels tighten reflexively. When you walk out of a cool restaurant into the hot outdoors, you sweat.

Since changes in somatic and autonomic functions usually are closely tied, the autonomic nervous system doesn't really function autonomously of the central nervous system. It does function automatically, unconsciously, and involuntarily. I prefer the phrase, automatic nervous system, but "autonomic nervous system" is deeply engrained in the tradition of medical physiology.

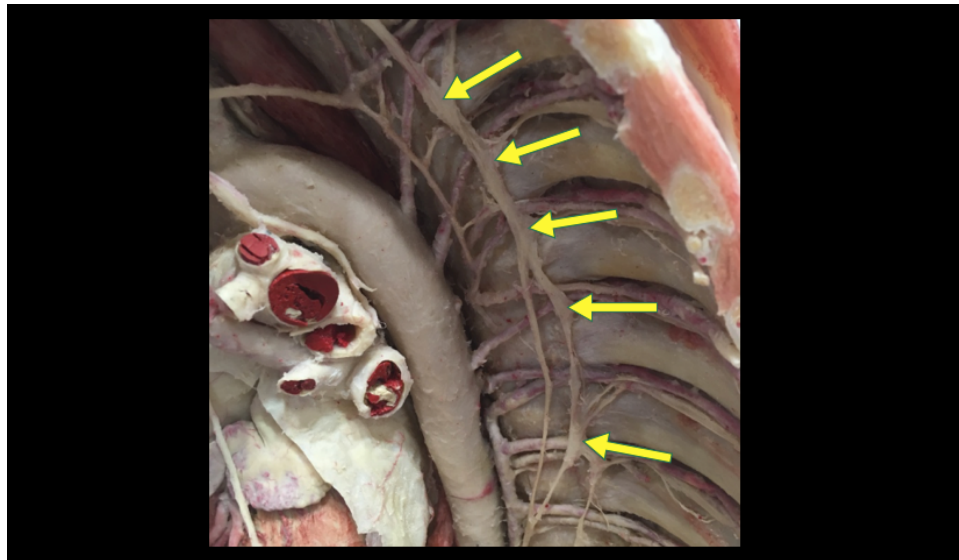


The ANS isn't autonomic in the sense of being autonomous of the brain. For instance, when you exercise, voluntary contraction of skeletal muscle is linked to automatic shifts in blood flow, resulting in appropriate delivery of fuel to and removal of products of metabolism from the exercising muscle.

THE UTILITY POLE OUTSIDE YOUR HOUSE

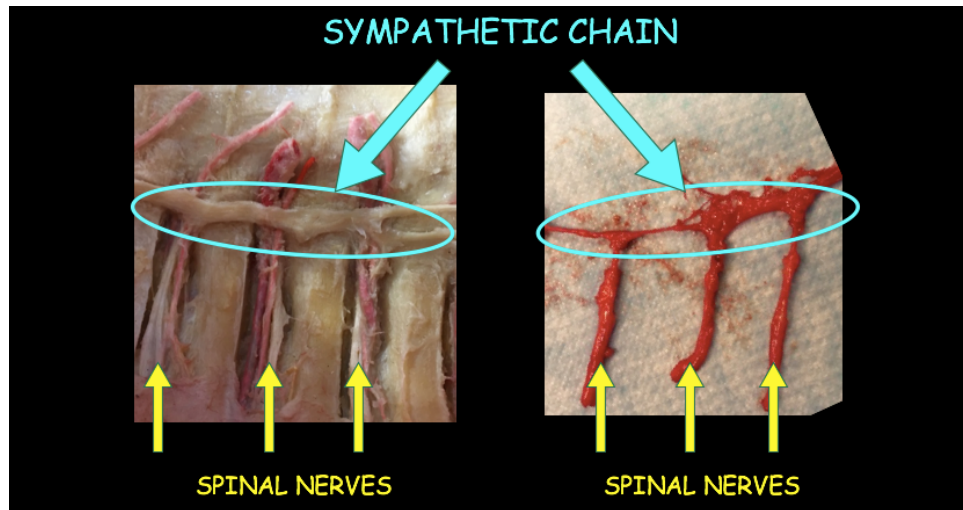
Nerves that travel to skeletal muscle and regulate movement come directly from the central nervous system. Nervous signals of the autonomic nervous system, however, travel indirectly to internal organs, via clumps of cells called “ganglia.”

Nervous signals of the autonomic nervous system come indirectly from the central nervous system, by way of clumps of cells called ganglia.

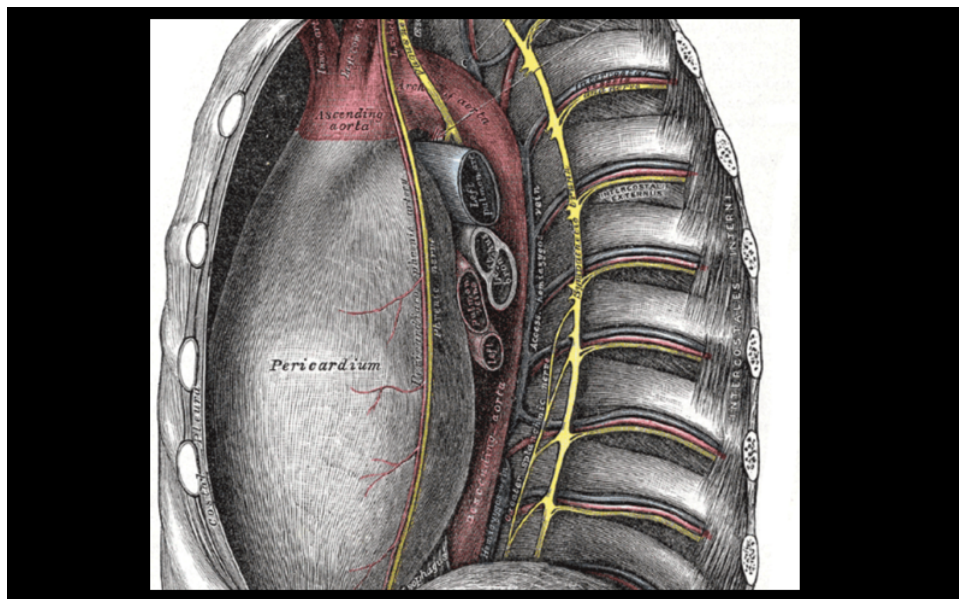


The sympathetic chain and ganglia (yellow arrows) in the back of the chest, in gullies on each side of the spinal column.

The ganglia are arranged like pearls on a string on each side of the spinal column. The nerve cells, the neurons, of the autonomic nervous system therefore are not in the brain or



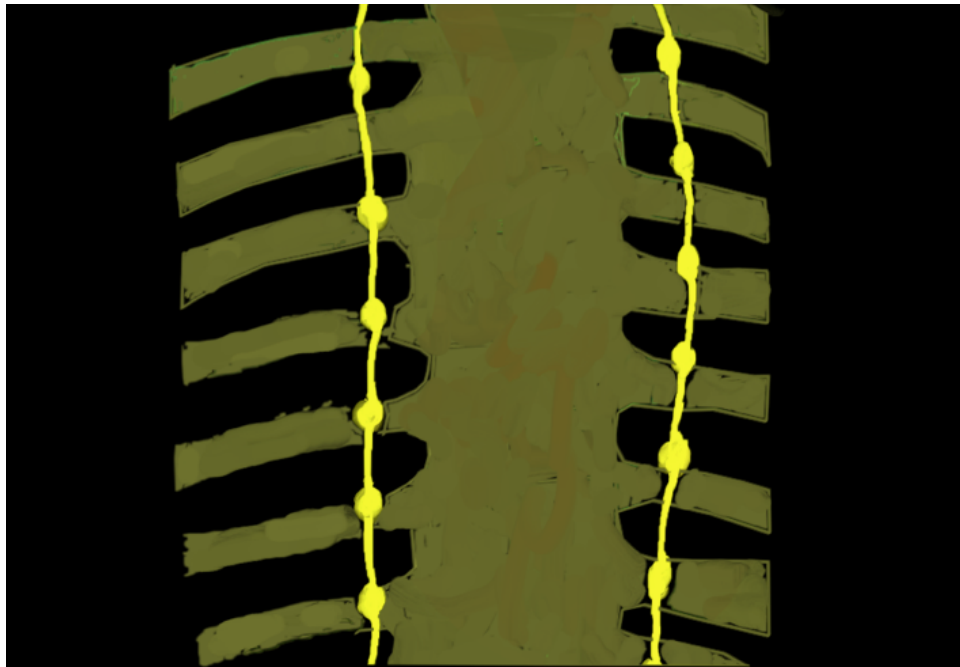
Plasticized and freshly harvested tissue showing the sympathetic chain at right angles to the spinal nerves.



Anatomy textbook diagram showing the sympathetic chain.

spinal cord.

This physical distinction originally led to the view that the nerves coming from the ganglia were functionally distinct from

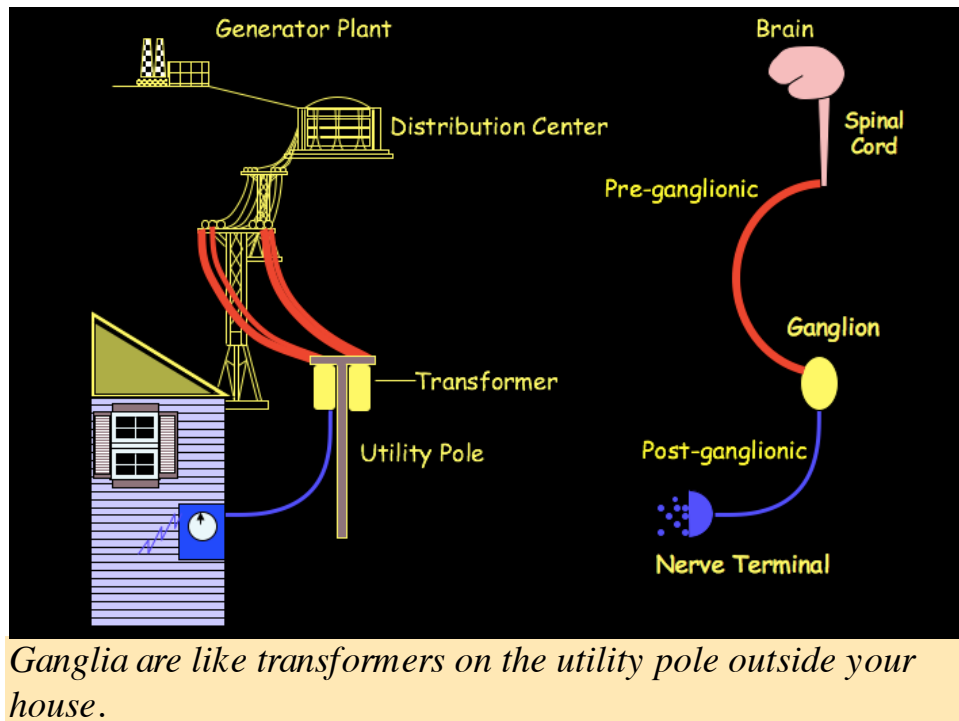


Autonomic ganglia are arranged like strands of pearls on each side of the spinal column.

the central nervous system—i.e., they were “autonomic.”

To convey what the ganglia of the autonomic nervous system do, think of how electricity is delivered to your home. From the generator plant and distribution center come thick, high voltage lines that transmit electricity along large towers. Outside your house is a utility pole that contains a transformer. From the utility pole, much thinner, low voltage wires connect to your house.

The ganglia act like transformer boxes. The nerves from the spinal cord are called “pre-ganglionic.” They are thick and conduct electricity quickly, because they have a myelin sheath. Myelin is a complex chemical consisting mainly of water, fat,



and protein that appears white to the eye. The “white matter” of the brain is white because of myelin, and myelinated nerves look white. Electric signals are conducted more rapidly in myelinated than in non-myelinated nerves. The nerves from the ganglia to the target organs are “post-ganglionic.” They are thin, slow conducting, and non-myelinated.

Just like the trunk lines to the utility pole outside your house are thick cables while the lines from the transformer to your house are thin wires, pre-ganglionic nerve fibers from the spinal cord to the ganglia are thick and conduct electricity rapidly, while post-ganglionic nerve fibers from the ganglia to most target organs are thin and transmit electricity slowly.

In keeping with the idea that adrenaline is an emergency

hormone that should be released rapidly, the cells of the adrenal gland that release adrenaline into the bloodstream receive myelinated, pre-ganglionic fibers, as if there were a direct wiring connection from the electrical distribution center to the terminal box.

HISTORY OF THE "AUTOMATIC" NERVOUS SYSTEM

On the Risk of Being a Physician's Son

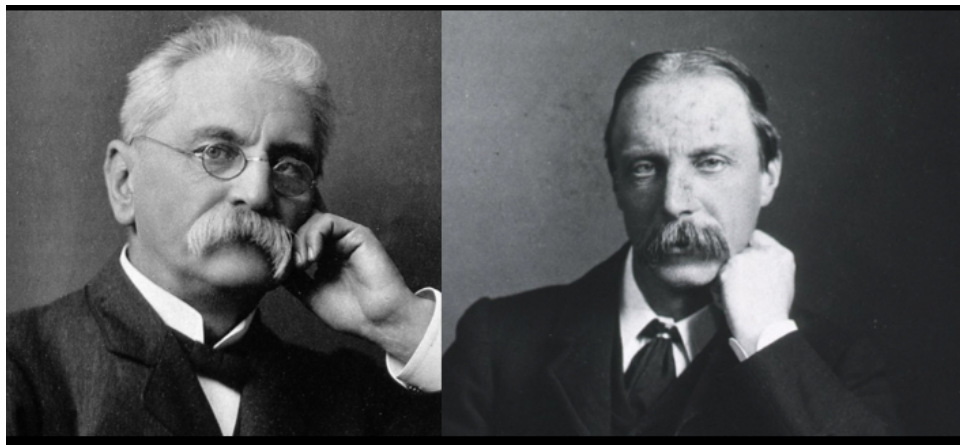
In the early 1890s, Dr. George Oliver, an English physician and amateur inventor, tested one of his homemade devices on his son. The device was supposed to measure the caliber of arteries. Oliver applied the device to his son's wrist at the radial artery, which carries blood to the hand. Oliver then administered an extract of adrenal gland to his son. The extract did appear to elicit constriction of the radial artery. Meanwhile, in London, Dr. E. A. Schäfer, a renowned Professor of Physiology at the University College, was carrying out experiments on laboratory animals, involving measurement of blood pressure by the height of a column of mercury in a tube connected to an artery. Oliver visited Schäfer's laboratory and brought with him a vial of the adrenal extract. Schäfer allowed injection of the material into the vein of a dog. This set the stage for one of the great discoveries in medical history.

The injection produced an immediate, startling increase in the animal's blood pressure, an increase so large that the column of mercury in the gauge actually overflowed the tube. In 1894 Oliver and Schäfer published the first report ever about the cardiovascular actions of an extract from a body organ.

According to Sir Henry Dale, an authority who received a Nobel Prize in 1936, the extract had been injected. According to others, based on the writings of both Oliver and Schäfer

themselves, the extract had been given orally.

At first glance this disagreement would seem trivial, but it isn't. An enzymatic "gut-blood barrier" prevents ingested catecholamines and related compounds from making their way into the bloodstream. Swallowed adrenaline is broken down efficiently by enzymes in the gut.



George Oliver and E.A. Schäfer, who first reported the cardiovascular actions of adrenal extract in 1894.

In fact, at least three enzymes carry out this crucial task. Moreover, most of the blood coming from the gut travels to the liver via the portal vein, and the liver also efficiently metabolizes catecholamines. One reason you can buy adrenal concentrate as a dietary supplement in health food stores is that after swallowing adrenaline solution, levels of the catecholamine itself in the general circulation hardly increase at all.

If you lacked one or more of the gut enzymes that detoxify catecholamines, however, or were taking a medication that

inhibited activities of the enzymes making up the “gut-blood barrier,” then ingesting adrenal concentrate could be disastrous.



Efficient metabolic breakdown of adrenaline in the gut and liver helps explain why you can buy adrenal concentrate as a dietary supplement.

On the other hand, adrenaline is extremely potent if it is injected so that it reaches the systemic circulation. As a college psychology major I conducted an experiment designed to test whether adrenaline augments emotional responses in rats. The experiment called for injecting adrenaline or, as a control, inactive saline solution under the skin. Adrenaline injection rapidly killed the animals; the appearance of blood on their snouts indicated lethal pulmonary edema due to sudden heart failure from extreme cardiac stimulation.

If Oliver had administered the extract directly by injection, he could well have killed his son.

What's in a Name?

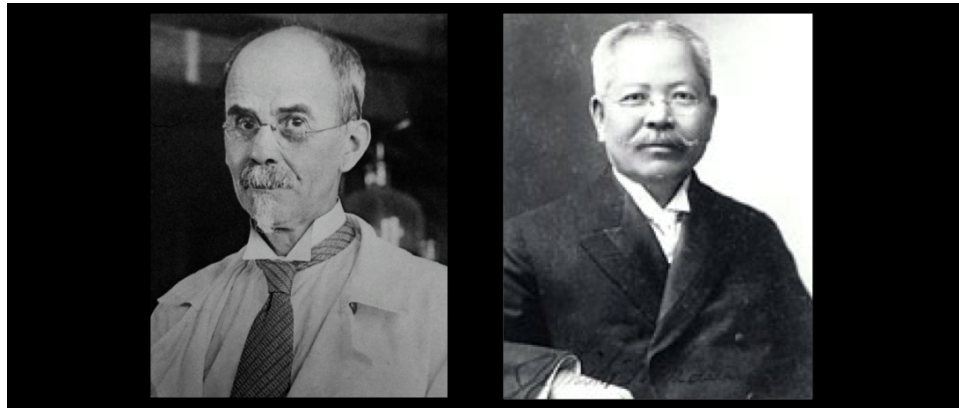
The most famous member of the catecholamine family has two names—adrenaline and epinephrine (EPI). Here is how this

came about.

Beginning immediately after Oliver and Schäfer reported the powerful effects of injected adrenal extract, researchers worldwide began a race to identify the “active principle” of the adrenal gland. One of these was John Jacob Abel, of Johns Hopkins, who devoted about a decade of his life to this project. Abel partially isolated a substance he called epinephrin, but this proved not to be epinephrine itself.

The first person to isolate the active principle of the adrenal gland was a chemist in the laboratory of the Japanese researcher and entrepreneur, Jokichi Takamine.

Takamine had set up a laboratory in New York City, under the patronage of Parke, Davis & Company.



John Jacob Abel and Jokichi Takamine raced to identify the active principle of the adrenal gland around 1900.

Keizo Uenaka, whom Takamine had hired as a chemist, successfully crystallized—and therefore isolated in pure form—what Takamine called adrenaline. In 1901, Takamine reported this first successful crystallization of a hormone. Almost

simultaneously, Thomas Aldrich, a colleague of Takamine at Parke-Davis (and, probably not coincidentally, a former assistant of Abel at Johns Hopkins), correctly deduced its chemical structure. Abel never published the correct chemical structure, and so medical historians gave Takamine and Aldrich the credit for two of the most important medical scientific feats ever—the first isolation in pure form and the first identification of the structure of a hormone.



J. Takamine, who discovered adrenaline, funded the Japanese cherry trees at the Tidal Basin in Washington, DC.

Indeed, this happened a few years before the word, “hormone,” was first used, by Ernest Starling in 1905. Starling discovered secretin, the first identified hormone, in 1902.

Adrenaline (trademarked as Adrenalin™) was the first natural substance to be patented (whether a natural substance is patentable continues to be an issue) and made Takamine rich. He founded three companies, one of which, Sankyo Pharmaceutical Company, continues to this day as Daiichi/Sankyo, the second largest drug company in Japan. Takamine also funded the gift of cherry trees that have graced the Tidal Basin in Washington, DC. Parke-Davis retained the trademark for Adrenalin.

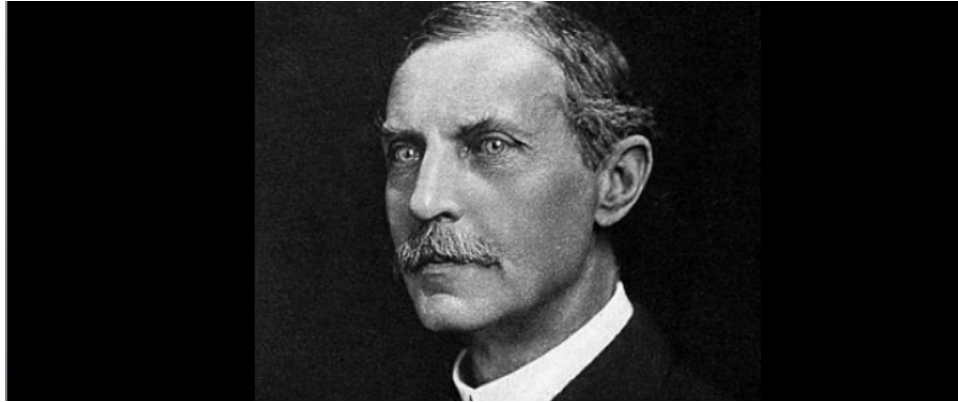
Abel continued to pursue his career goal of identifying, isolating, and purifying hormones. He helped found the American Society for Pharmacology and Experimental Therapeutics and served as editor of the society's official journal, the Journal of Pharmacology and Experimental Therapeutics (JPET). He also founded the Journal of Biological Chemistry (JBC). JPET and JBC are still among the most prestigious journals in pharmacology and biochemistry. To this day, scientific reports in American journals, such as JPET, use the word that Abel introduced, “epinephrine,” whereas European journals commonly use Takamine's “adrenaline.” In this book I use epinephrine (EPI) and adrenaline interchangeably.

Langley's "Autonomic Nervous System"

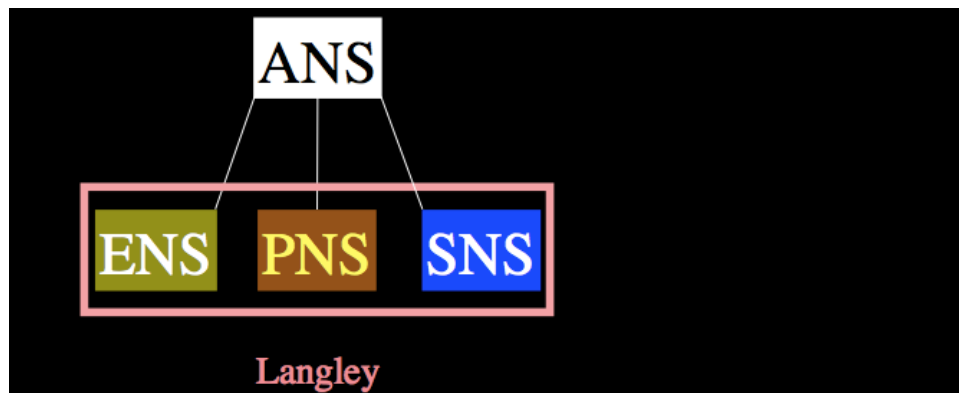
About the turn of the 20th century, the English physiologist, John Newport Langley, consolidated diverse findings from his and others' research to propose the concept of the “autonomic nervous system” (ANS). Langley invented this phrase.

By this term Langley was referring to networks of nerves outside the central nervous system that derive from ganglia and influence body processes. “Autonomic” reflected Langley's view that the networks seemed to function autonomously of the central nervous system. He described three components of the autonomic nervous system—sympathetic, parasympathetic (a word he invented), and enteric—sympathetic nerves derived from the thoraco-lumbar spinal cord, parasympathetic from the brainstem and sacral spinal cord, and enteric in walls of the

gastrointestinal tract.

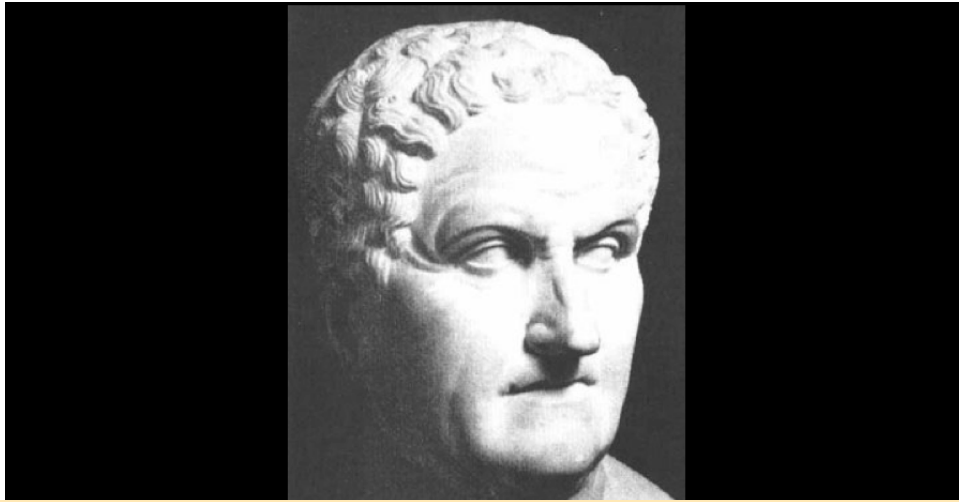


John Newport Langley (1852-1925), father of the “autonomic nervous system.”



Langley’s “autonomic nervous system” (ANS) consists of the enteric nervous system (ENS), parasympathetic nervous system (PNS), and sympathetic nervous system (SNS).

The third part of Langley’s autonomic nervous system is the sympathetic nervous system. This term he didn’t invent. Instead, the phrase, “sympathetic nervous system,” goes back to ancient times—to the teachings of Galen, the 2d century Greek physician whose ideas and teachings dominated medical thought and practice for 14 centuries.



Galen (ca. 129-216), father of the “sympathetic nervous system”

Galen taught that the body has “spirits”—animal, vital, and natural. He viewed the nerves as conduits for delivering the animal spirits to body organs. The organs would then function in harmony with each other, in concert with each other—in “sympathy” with each other. No one ever has come up with evidence for the existence of the spirits; however, the idea that the sympathetic nervous system coordinates functions of body organs is essentially correct.

As will be seen, the sympathetic nervous system can be divided into three parts based on the main chemical messengers involved.

The Heart of a Frog

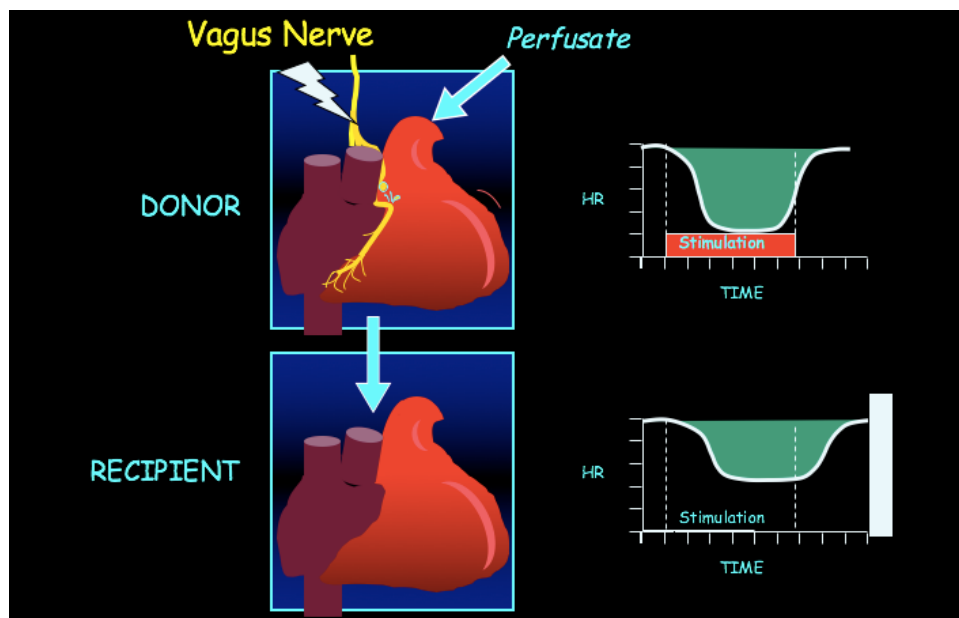
One of the most famous experiments in medical history—an experiment that led to a Nobel Prize for the investigator, Otto

Loewi—was based on the heart of a frog.

The experimental setup consisted of the exposed, beating hearts of two frogs, a “donor” frog and a “recipient” frog. Loewi perfused the heart of the donor frog with a fluid that was led to the beating heart of the recipient frog.



Otto Loewi (Nobel Prize, 1936)



Loewi's experimental setup to demonstrate that stimulation of the vagus nerve releases a chemical messenger.

When he electrically stimulated the vagus nerve to the heart of the donor frog, the heart rate decreased. The stimulation also decreased the heart rate of the recipient frog, implying that the stimulation released something into the perfusion fluid delivered from the donor heart to the recipient heart.

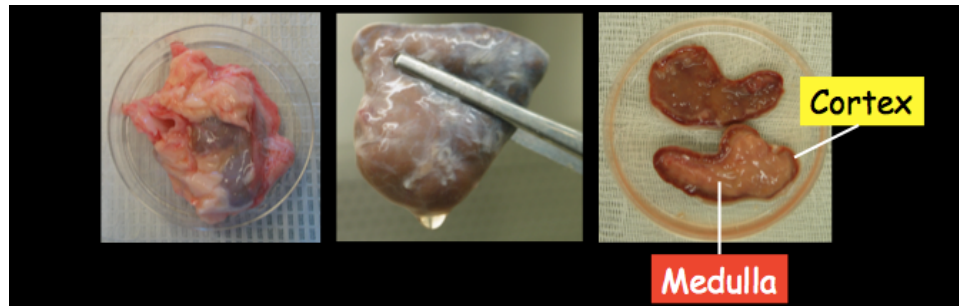
Loewi inferred that the nerve stimulation released a chemical substance that caused the recipient frog's heart to slow down too. He called the substance "*Vagusstoff*" or "substance of the vagus." He then showed that the *Vagusstoff* produced a variety of responses in other tissues that were identical with those produced by a chemical, acetylcholine. In 1926 Loewi and a coworker identified the *Vagusstoff* as acetylcholine.

Otto Loewi was the first person to demonstrate the existence of a chemical messenger coming from nerves—a neurotransmitter. He identified the neurotransmitter as acetylcholine. For this he received a Nobel Prize.

In his Nobel Lecture in 1936, Loewi claimed he had also proven that adrenaline is the neurotransmitter of the sympathetic nerves. Others had found that adrenaline, in the presence of oxygen and alkali, produces a green fluorescence. Loewi reported that in his preparation the heart perfusate coming from the stimulated heart showed this reaction. He considered this to be proof that adrenaline is the chemical messenger of the sympathetic nerves. He was wrong. At the time it was not appreciated that other catecholamines (in particular, norepinephrine) give off the same green fluorescence.

The Fat above the Kidneys

A couple of decades after Langley formulated his idea of the autonomic nervous system, the American physiologist, Walter B. Cannon, added what can be considered to be a fourth component of the ANS—the sympathetic adrenergic system (SAS). This is the part of the autonomic nervous system where adrenaline is released from the inner part (medulla, from the Latin word for “marrow”) of the adrenal gland. The outer part, the cortex (from the Latin word for “bark,” as in the bark of a tree) is the source of a variety of steroid hormones. The SAS is a form of neuroendocrine system.

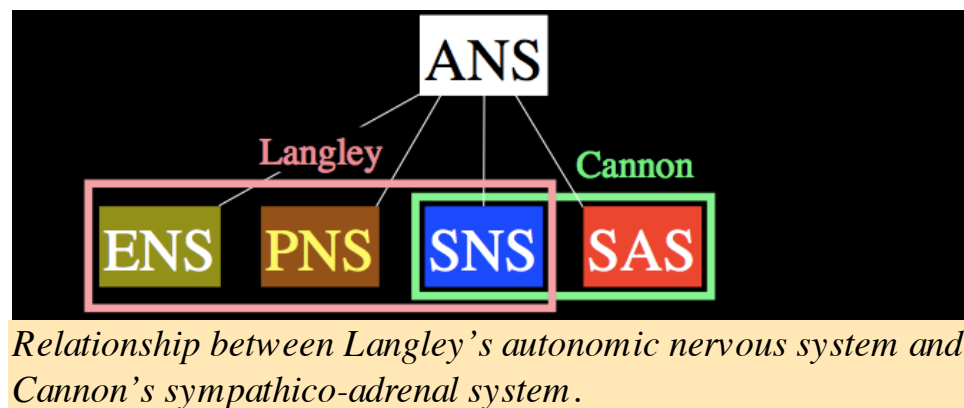


The adrenal glands are in the fat above the kidneys. The medulla contains adrenaline. The cortex contains steroids.

No one knew of the existence of the adrenal glands until Bartholomeo Eustachius (for whom the eustachian tube is named) described their anatomy in 1563, but there may have been a hint from a much older source. The Hebrew Bible, in Exodus and Leviticus, describes in detail the rituals of animal sacrifice. Some tissues were specified for ritual burning; eating them was strictly forbidden. One of these tissues was the “fat above the kidneys.” The text stipulates—not once but thirteen times—that the fat above the kidneys was to be burned and not

to be eaten by anyone.

Why was eating the fat above the kidneys proscribed? The fat above the kidneys is unique for its contents, because buried within it are the adrenal glands, which store the powerful adrenocortical hormones, cortisol, aldosterone, and adrenal androgens, and the even more powerful adrenomedullary hormone, adrenaline. Depending on the efficiency of metabolic breakdown of these chemicals in the gut, eating adrenal gland tissue could result in entry of one or more of these physiologically active compounds into the bloodstream. Ingestion of adrenal gland tissue repeatedly by the priests over a long period could have made them ill or killed them.



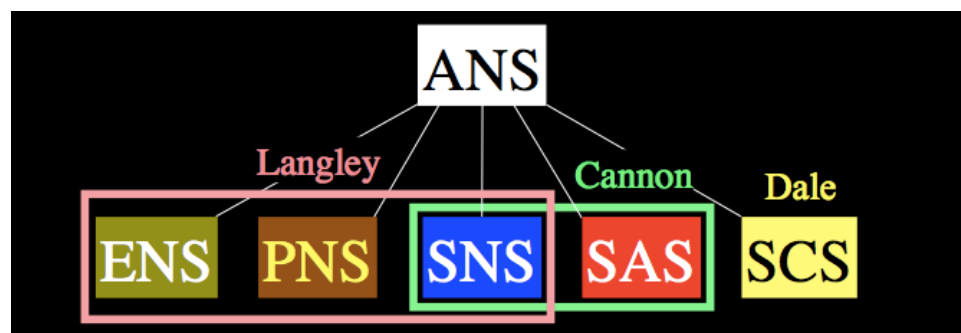
Cannon taught that the sympathetic nervous system and adrenal gland act as a functional unit in emergencies. This functional unit is sometimes called the “sympathico-adrenal” system or “sympathoadrenal system.”

According to Cannon, the sympathoadrenal system mediates bodily changes in “fight-or-flight” situations. (“Fight or flight” is a phrase he introduced.) He viewed the sympathoadrenal

system as the key effector for maintaining “homeostasis,” a word he invented.

Dale's Sympathetic Cholinergic System

In the 1930s Sir Henry Dale (Nobel Prize, 1936) added what may be considered a fifth component of the autonomic nervous system, the sympathetic cholinergic system, or SCS. The sympathetic cholinergic system is the main ANS component involved with sweating when you are exposed to environmental heat (thermoregulatory sweating).



The sympathetic cholinergic system (SCS)

The Brains of the Operation

In 1863, Claude Bernard reported that cutting the cervical spinal cord produced an immediate, marked drop in blood pressure. This probably was the first evidence that the brain regulates overall cardiovascular “tone.”

In 1883, Ivan Pavlov reported his studies showing that the “centrifugal nerves of the heart” accelerated and augmented heart contraction. The nerves were traced to their source in the

lateral horns of the spinal cord. At about the same time, other investigators noted the indirect, reflexive cardiovascular effects of stimulating neural pathways traveling to the brain. In 1836, Sir Astley Cooper showed that occluding the common carotid arteries increased blood pressure and heart rate, and in 1900 Siciliano proposed that a signal to the brain comes from the region of where the carotid artery splits into the internal and external carotid arteries.

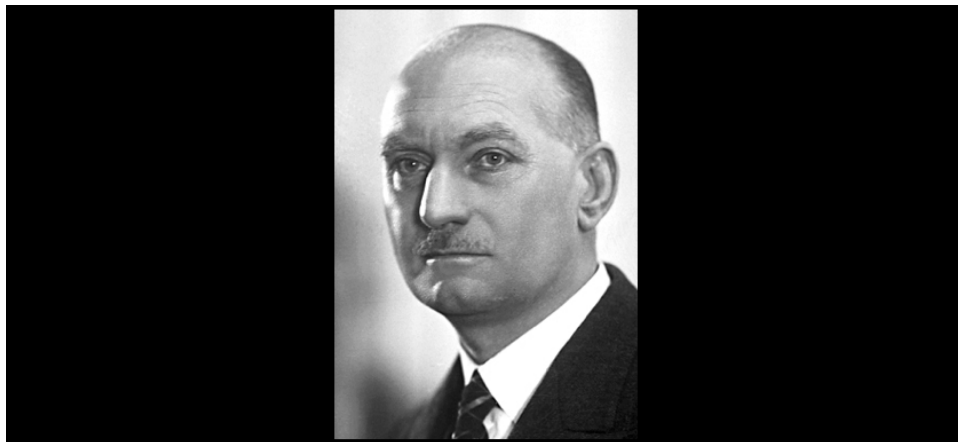
In 1923, Heinrich Hering found that mechanical stimulation of the wall of the carotid sinus, a small area of dilatation in the region of the carotid bifurcation, produced marked decreases in heart rate and blood pressure—and the “baroreflex” was born. The carotid sinus nerve (also called “Hering’s nerve”) travels in the glossopharyngeal nerve (the ninth cranial nerve) to the lower brainstem.

After Hering’s discovery of the carotid sinus nerve, the Belgian physiologist Corneille Heymans (along with his father, J. F. Heymans) studied reflexive regulation of breathing based on afferent input to the respiratory center in the brainstem from the carotid sinus region. The experiments exploited an extraordinary preparation developed by the senior Heymans that made it possible to keep alive the completely isolated head of a dog by perfusion of blood from another dog, while the body was also kept alive with the help of artificial respiration. This meant that the only communication between the head and the rest of the body was provided by the nerves.

Heymans showed that when the lungs expand, inspiration reflexively ceases, and when the lungs are collapsed, inspiration reflexively is stimulated (the Hering-Breuer reflex). If the

tension of carbon dioxide in the arterial blood to the head increased, or the oxygen tension decreased, ventilation increased reflexively (the chemoreflex).

Heymans also demonstrated that high blood pressure at the carotid sinus reflexively relaxes blood vessels and decreases the heart rate (the arterial baroreflex). He also proposed that the carotid sinus baroreflex modifies adrenomedullary secretion reflexively.



Corneille Heymans received a Nobel Prize in 1938 for his studies of chemoreflexes regulating breathing and baroreflexes regulating blood pressure.

Heymans therefore described what can be depicted by a two-by-two table, in which increasing carbon dioxide tension or decreasing oxygen tension in the carotid arterial blood not only reflexively increases respiration, via chemoreceptors in the carotid body, but also constricts blood vessels and increases heart rate; and increasing carotid arterial pressure not only relaxes blood vessels and slows heart rate but also decreases respiration, via carotid sinus stretching and baroreceptor stimulation. For this work Heymans received a Nobel Prize in

$\uparrow pCO_2 / \downarrow pO_2$ \uparrow Carotid P	
Chemoreceptor Stimulation	Baroreceptor Stimulation
\uparrow Ventilation	\downarrow Ventilation
\uparrow BP	\downarrow BP

2 X 2 table showing Heymans's findings about the chemoreflex and baroreflex

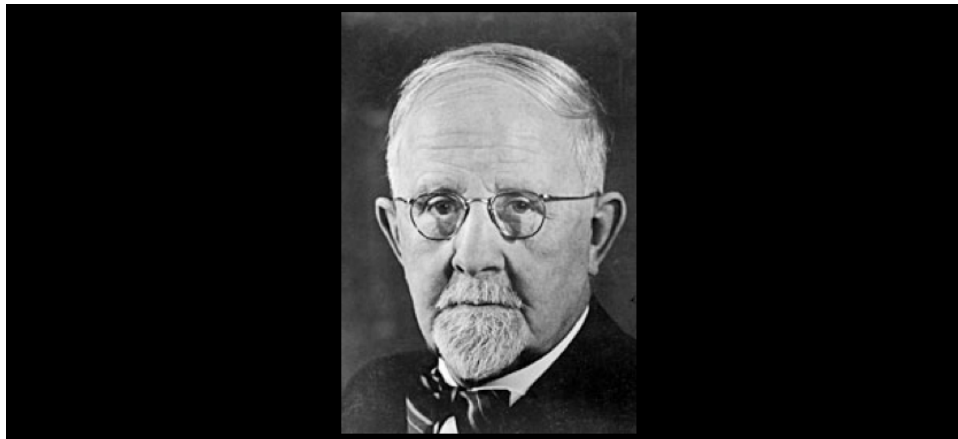
1938.

Cannon studied not only peripheral autonomic systems but also sites in the brain that regulate them. In the 1920s he noted that removal of the cerebral cortex evoked rage behavior, accompanied by high blood glucose levels; decorticated adrenalectomized animals exhibited the same behavior, but without hyperglycemia. These findings fit with cortical restraint of primitive emotional behaviors and of emotion-associated adrenaline release. Cannon's student, Philip Bard, obtained evidence that physiological concomitants of primitive emotions originate in the hypothalamus.

Bard directed the Department of Physiology at Johns Hopkins for 31 years and was an Emeritus Professor when I was a medical student there.

In the 1920s to 1930s the Swiss physiologist Walter Rudolf Hess focused on the functional organization of the hypothalamus with respect to the regulation of parasympathetic and sympathetic outflows. He showed that stimulation of the

same hypothalamic sites that altered functions of internal organs via sympathetic outflows (pupillary dilation, hair bristling, and tachycardia) also evoked particular behaviors that seemed to be directed outwards towards the environment (“ergotropic” effects). In contrast, stimulation of other sites evoked slow heart rate, salivation, pupillary constriction, vomiting, urination, and defecation, consistent with generalized parasympathetic activation. These autonomic effects also were associated with particular behaviors (e.g., postural change associated with defecation). Hess viewed these changes as protection against a kind of internal overloading (“trophotropic”). The sympathetic-ergotropic and parasympathetic-trophotropic areas operated as if they were in a dynamic state of equilibrium. For this work Hess received a Nobel Prize in 1949.



W. R. Hess received a Nobel Prize in 1949 for his research on regulation of autonomic outflows from the hypothalamus.

Hess’s experiments based on local electrical stimulation took place before the beginning of the era of chemical neuroanatomy. In 1954 Marthe Vogt noted large regional differences in concentrations of norepinephrine (still termed

“sympathin” at the time) in the brain. This heterogeneity could not be explained by norepinephrine in blood vessel walls and suggested the existence of norepinephrine as a neurotransmitter in particular brain areas.



Marthe Vogt, a pioneer of brain catecholamine neurochemistry and neuroanatomy.

Annica Dahlstrom and Kjell Fuxe subsequently described catecholamine pathways and centers that were distinct from traditional neuroanatomic tracts and nuclei.

The generally accepted view from the 1950's until the 1970's was that the summed activity of diffusely interconnected fibers of the “reticular activating system” in the brainstem randomly generated autonomic outflows, as if there were an impenetrable neuronal thicket that intervened between interoceptive input and autonomic output from the brain.

Several developments forced abandonment of this position. First, most interoceptive inputs to the brain were found to terminate in a specific cluster of cells in the dorsomedial

medulla, the nucleus of the solitary tract (NTS).

Second, another small collection of neurons in the rostral ventrolateral medulla (RVLM) was found to be a major source of descending projections to the sympathetic pre-ganglionic neurons in the lateral horns of the spinal cord. Third, tract tracing experiments showed that ascending and descending information between the lower brainstem and higher centers travels in extensively branching (“arborized”) fibers among relatively few clusters of neural cells, rather than in a diffuse reticular system. And fourth, neurophysiological studies demonstrated that pre-ganglionic sympathetic neurons discharge rhythmically, the rhythmic discharges depending importantly on lower brainstem networks of coupled oscillators generating that generate the rhythm inherently—a pacemaker for sympathoneural outflow.

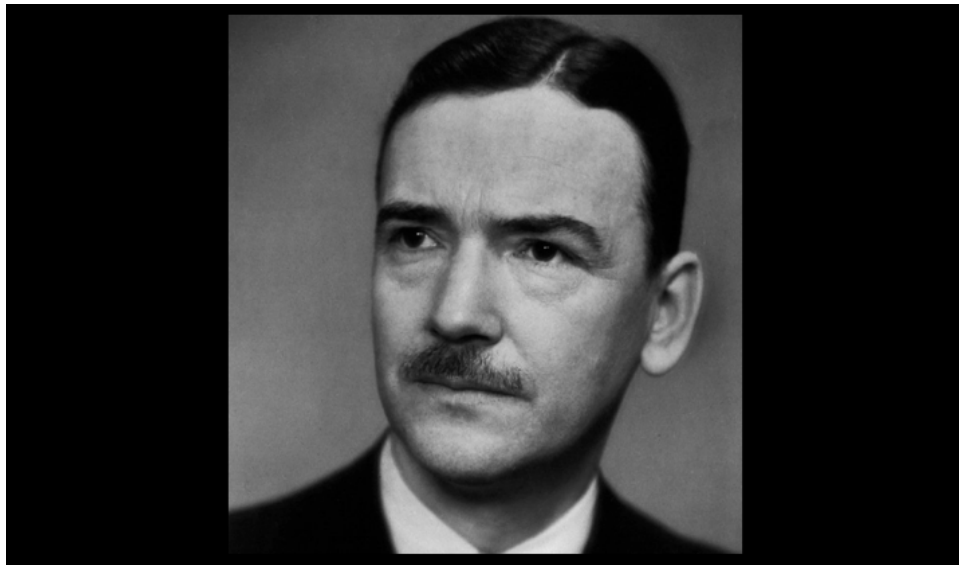
Third, the findings of Dahlstrom and Fuxe demonstrating specific catecholaminergic pathways led to fundamentally new ideas about functional connections in the brain and ushered in the era of “chemical neuroanatomy.”

Over the next half century, neurochemical pathways participating in autonomic outflows were described in detail. Adding to the rich diversity, Tomas Hökfelt subsequently reported evidence for co-storage of peptides with catecholamines in brainstem neurons, and Geoffrey Burnstock introduced the concept of purinergic autonomic nerves. The field of “chemical coding” based on co-transmission continues to evolve.

The Nobel Chemicals

Catecholamine research has led to many Nobel Prizes.

Discoveries based on catecholamine research relate directly to regulation and dysregulation of the inner world by the autonomic nervous system and development of several novel, successful, rational treatments for major diseases. This section presents some of these discoveries together, to introduce ideas that receive more attention in future sections and to affirm the continuing importance of catecholamine systems in science and medicine.

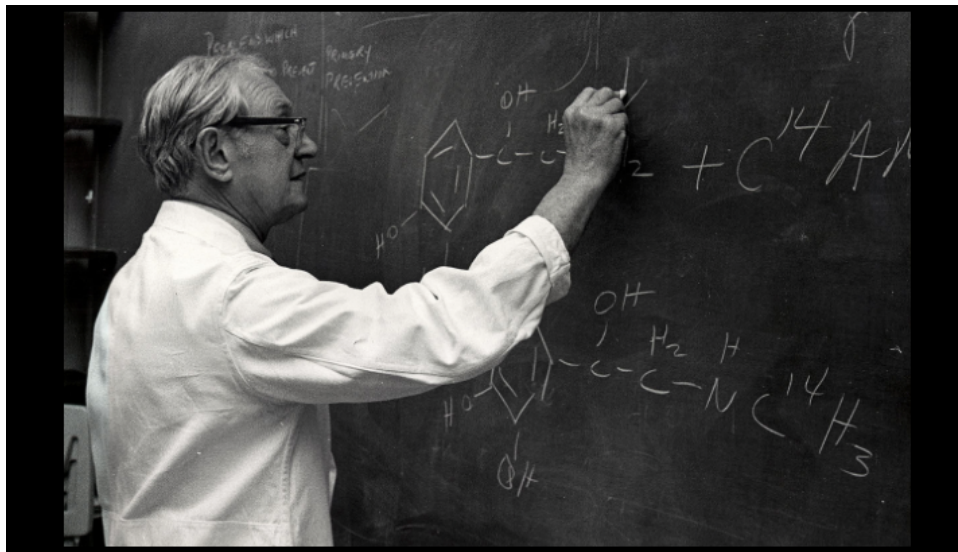


U.S. von Euler (Nobel Prize, 1970) identified norepinephrine as the neurotransmitter of the sympathetic nervous system.

In the mid-1940s, Ulf Svante von Euler identified the neurotransmitter of the sympathetic nerves in mammals as not adrenaline, which Loewi and Cannon had proposed, but

norepinephrine (synonymous with noradrenaline). For this discovery von Euler received a Nobel Prize in 1970.

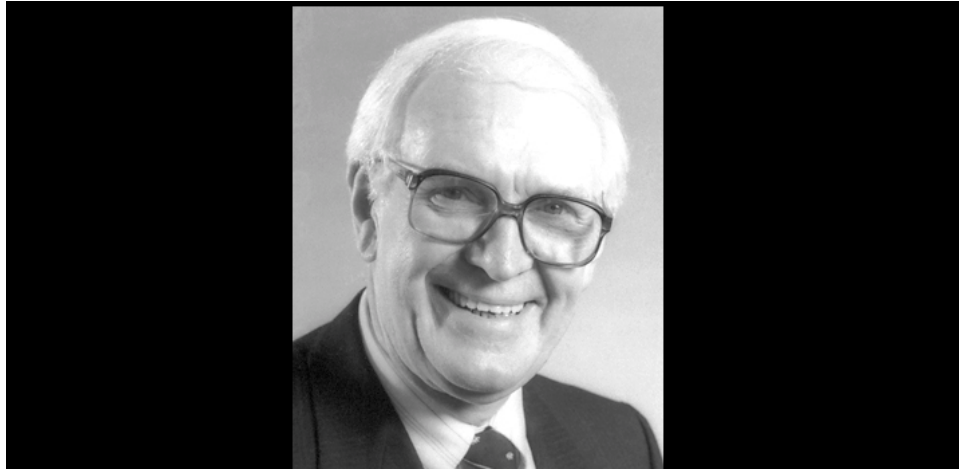
After release of norepinephrine from sympathetic nerves, the norepinephrine undergoes inactivation mainly by a conservative recycling process, in which sympathetic nerves take up norepinephrine from the fluid bathing the cells--a process called uptake-1. Once back inside the nerve cells, most of the norepinephrine undergoes uptake back into storage vesicles. Julius Axelrod's studies—in Building 10 at the NIH—about the disposition of catecholamines introduced the idea that termination of the actions of some neurotransmitters depends on neuronal reuptake. Axelrod and von Euler shared the 1970 Nobel Prize in Physiology or Medicine.



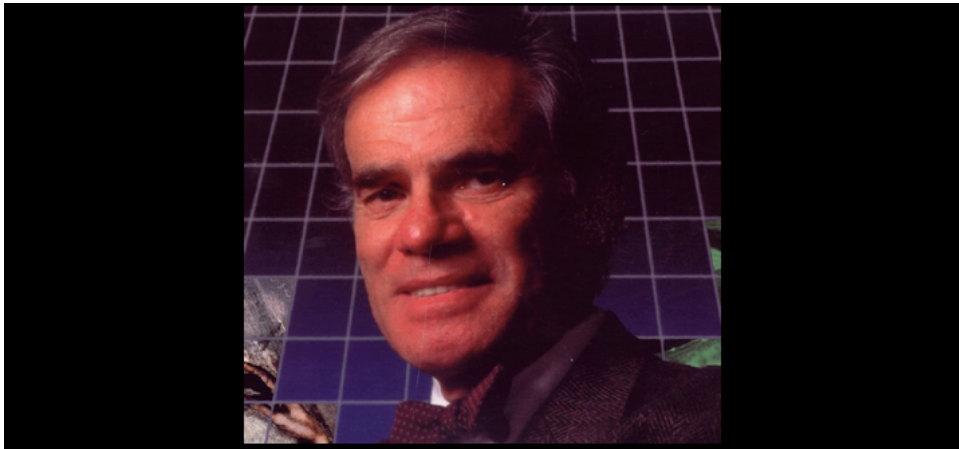
Julius Axelrod (Nobel Prize, 1970) discovered neuronal reuptake as a route of catecholamine inactivation.

After Raymond Ahlquist's 1948 suggestion that there were two types of adrenoceptors, alpha and beta, researchers worldwide

directed their attention to development of novel treatments for diseases based on drugs that block or stimulate adrenoceptors. For the development of beta-adrenoceptor blockers, Sir James Black shared a Nobel Prize in 1988.



Sir James W. Black (Nobel Prize, 1988) developed a class of catecholamine receptor blockers.



Martin Rodbell (shown here) and Alfred G. Gilman shared a 1994 Nobel Prize for discovering G-proteins.

Discoveries related to the mechanisms determining cellular

activation after adrenoceptor occupation have led to at least three other Nobel Prizes. For the discovery of cAMP, the first identified intracellular messenger (“second messenger”), E. W. Sutherland received a Nobel Prize in 1971. For the discovery of phosphorylation as a key step in the activation or inactivation of cellular processes, Edmond H. Fischer and Edwin G. Krebs shared a Nobel Prize in 1992. For the discovery of G-proteins, Alfred G. Gilman and Martin Rodbell shared a Nobel Prize in 1994.

Arvid Carlsson and Paul Greengard shared a Nobel Prize in 2000. Both these scientists focused on the “third catecholamine,” dopamine.



Arvid Carlsson (Nobel Prize, 2000) discovered that dopamine is a neurotransmitter in the brain.

Until about the 1950s, dopamine had been assumed not to have any specific function in the body beyond serving as a chemical intermediary in the production of adrenaline and norepinephrine. Carlsson discovered that dopamine in the brain

acts as a neurotransmitter in its own right and is of great importance in regulation of movement. Loss of dopamine in a particular pathway in the brain produces the movement disorder defining Parkinson's disease, and replenishment of dopamine by administration of its precursor, L-DOPA, results in rapid improvement in movement. Carlsson also demonstrated that effective drugs to treat schizophrenia work by blocking dopamine receptors in the brain.

Greengard discovered that communication between nerve cells mediated by catecholamines takes place by a relatively slow, diffuse process, called slow synaptic transmission. This process probably underlies phenomena such as mood and vigilance and also modulates fast synaptic transmission, which is involved with rapid phenomena such as speech, movement, and sensation.



Paul Greengard (Nobel Prize, 2000) discovered slow transmission of signals after dopamine binds to its receptors.

Release of norepinephrine in response to traffic in sympathetic nerves depends on the existence of functional sympathetic

nerve terminals. The development and continued existence of sympathetic nerves in an organ depend in turn on a continuous supply of a nerve growth factor.

The discovery of nerve growth factor arose importantly from studies of sprouting of nerve filaments from sympathetic ganglia cells. For describing the first known neurotrophic factor, Stanley Cohen and Rita Levi-Montalcini shared a 1986 Nobel Prize.

The most recent Nobel Prizes for catecholamine research were awarded in 2012 to Robert Lefkowitz and Brian Kobilka, for their discoveries about catecholamine receptors (adrenoceptors) and more generally about a class of receptors, which include adrenoceptors, that function by coupling to G-proteins. Lefkowitz isolated beta-adrenoceptors, and Kobilka identified the genes that encode types of beta-adrenoceptors.



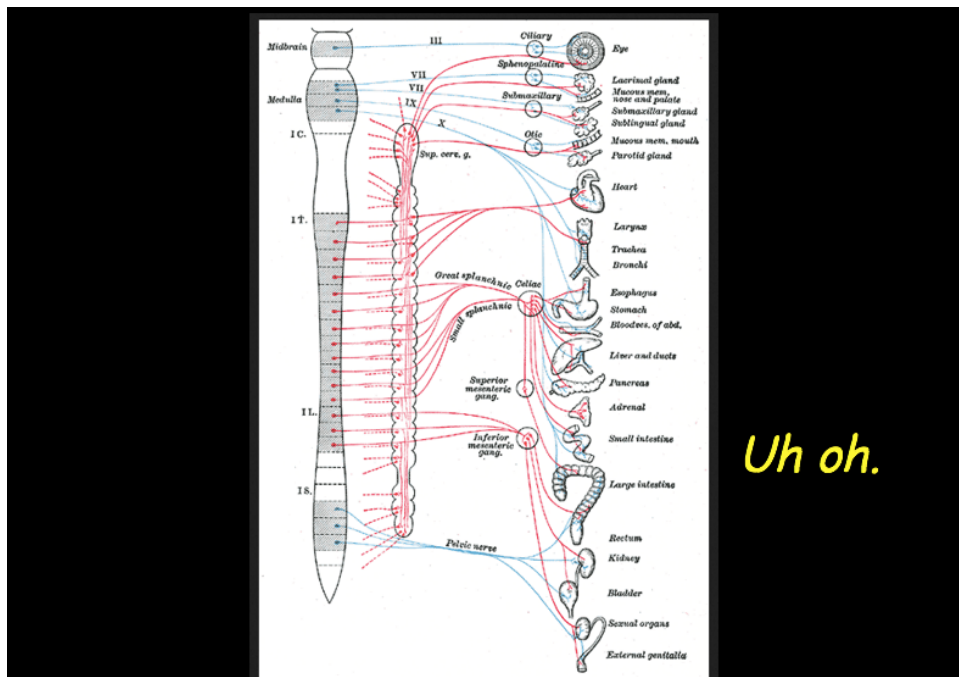
Rita Levi-Montalcini (Nobel Prize, 1986) discovered nerve growth factor, which sympathetic nerves require.



Robert Lefkowitz discovered G-protein coupled receptors by studying catecholamine receptors. Brian Kobilka identified genes encoding catecholamine receptors. They shared the 2012 Nobel Prize in Chemistry.

ORGANIZATION OF THE ANS

The autonomic nervous system is not one thing. It has parts. Langley's autonomic nervous system consists of the enteric nervous system (ENS), the parasympathetic nervous system (PNS), and the sympathetic nervous system. Cannon added a component, the sympathetic adrenergic system (SAS), and Dale added a component, the sympathetic cholinergic system (SCS). That is, there are three component sub-systems of the sympathetic nervous system, depending on the chemical messenger. You've also learned that autonomic nerves pass through ganglia, so that there are pre-ganglionic and post-ganglionic autonomic nerves.



Uh oh.

A classical diagram of the autonomic nervous system.

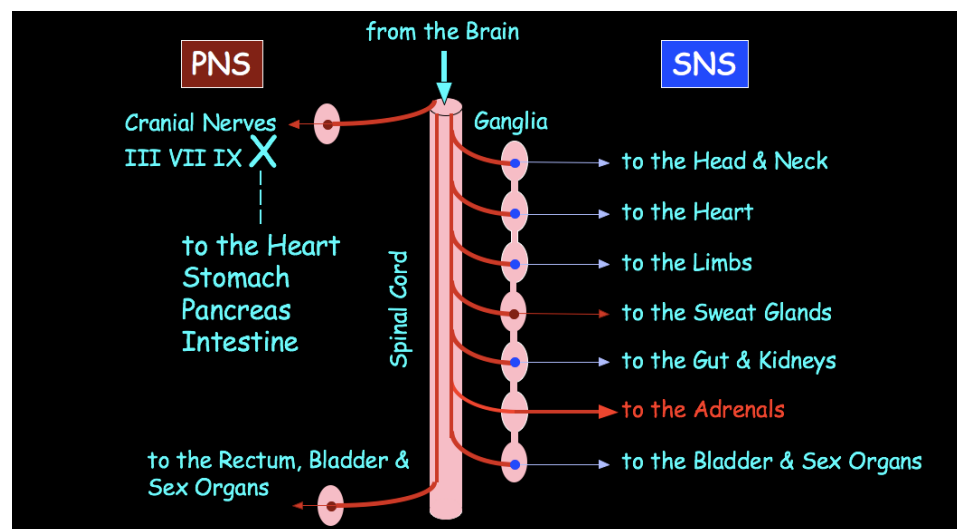
Now it's time to consider how the components of the

autonomic nervous system are distributed in the body. Here is a classical diagram of the autonomic nervous system. After looking this over for a few seconds, my guess is you would say, “Uh oh.”

The organization of the autonomic nervous system seems impossibly complex.

I hope you remember the analogies of the Tootsie Roll pop, pearls on a necklace, and the transformer on the utility pole outside your house. If you have these in mind, then you have a foundation for learning how components of the ANS are distributed in the body.

Distribution of the ANS in the Body



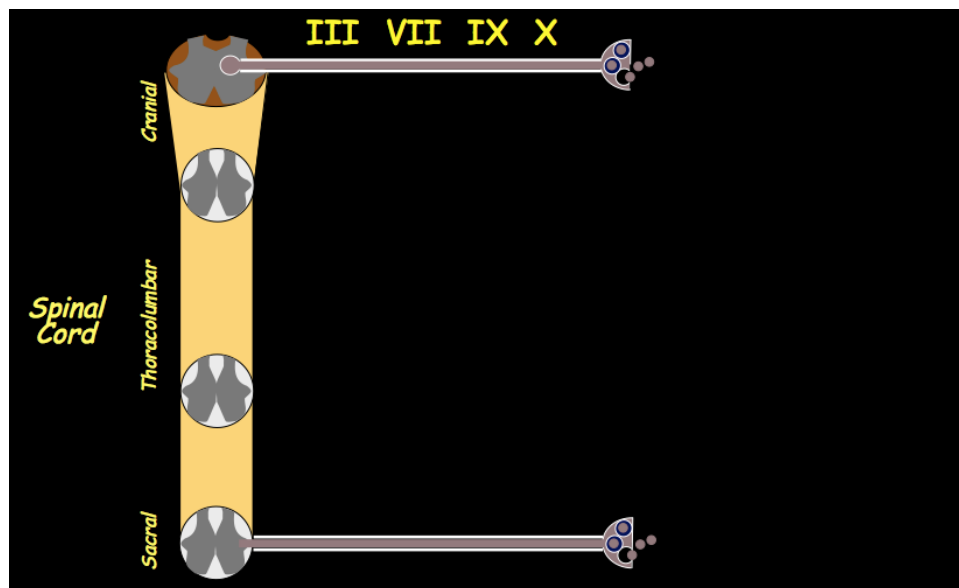
Autonomic nerves come from the brainstem and spinal cord.

The spinal cord is divided into sections. The section in the neck is cervical. Below that is the thoracolumbar spinal cord, and at

the bottom is the sacral spinal cord. The autonomic nerves come from the brainstem as cranial nerves and from the thoracolumbar and sacral spinal cord. The autonomic nerves coming from the thoracolumbar spinal cord are sympathetic nerves. The autonomic nerves coming from the brainstem and sacral spinal cord are parasympathetic nerves.

THE PARASYMPATHETIC NERVOUS SYSTEM (PNS)

The parasympathetic nervous system regulates “vegetative” body functions—things you do at night or behind closed doors.



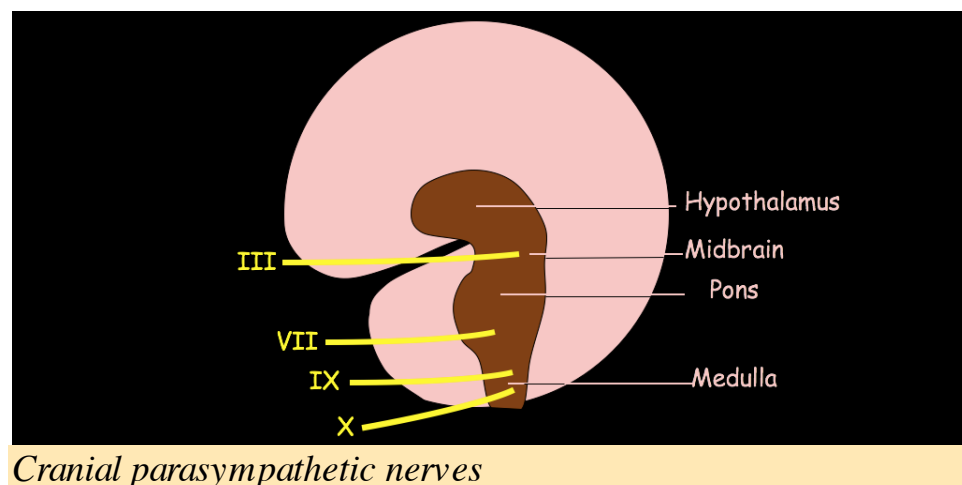
Parasympathetic nerves come from the brainstem and from the bottom of the spinal cord.

The parasympathetic nervous system (abbreviated as PNS) in some ways acts like the opposite of an emergency system.

Increased activity of this system is associated with “vegetative” behaviors, activities that increase instead of use up energy. Examples are sleeping, eating, salivating, and digesting.

The upper part of the parasympathetic nervous system is the nerves that come from the brainstem. Most of the nerves of the parasympathetic nervous system come from the brainstem. These nerves travel to many parts of your body, including the eyes, face, tongue, heart, and most of the gastrointestinal tract.

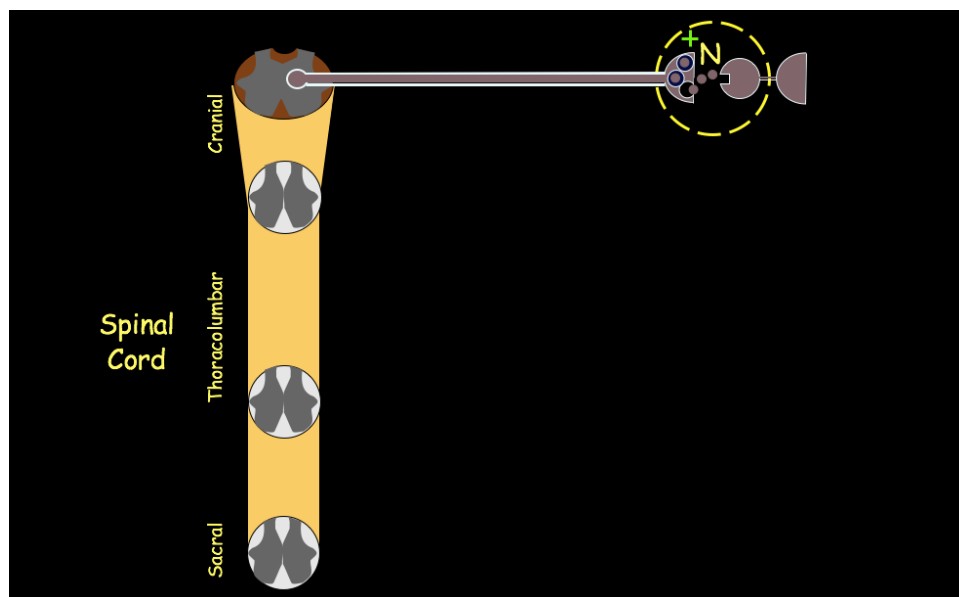
The nerves that come from the brainstem are called the cranial nerves. (“Cranial,” comes from the Greek and Latin words for “skull.”) The parasympathetic nerve fibers travel in cranial nerves that have specific names. The oculomotor nerve (the 3rd cranial nerve) connects to the eyes, the facial nerve (the 7th cranial nerve) to the face, the glossopharyngeal nerve (the 9th cranial nerve) to the tongue and muscles involved in swallowing and talking, and the vagus nerve (the 10th cranial nerve) to the heart and most of the abdominal organs.



Stimulation of the parasympathetic fibers in the head causes the

pupils to constrict, the lacrimal glands to secrete tears, and the salivary glands to secrete watery saliva. Note that the parasympathetic fibers to the face are peripheral, even though they travel in cranial nerves.

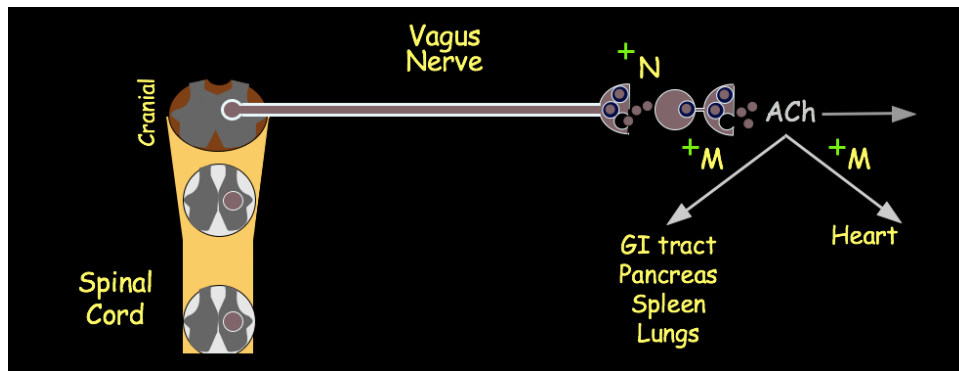
The neurotransmitter in all the autonomic ganglia is acetylcholine. Acetylcholine binds to nicotinic receptors (+N) on the cell bodies of the post-ganglionic nerves. Acetylcholine is also the chemical messenger released from the post-ganglionic parasympathetic nerve terminals in the target organs. The receptors in the target organs are muscarinic (+M).



Parasympathetic nerves: Long myelinated pre-ganglionic, short non-myelinated post-ganglionic. Acetylcholine acting at nicotinic receptors (+N) mediates ganglionic neurotransmission.

The vagus nerve is the tenth cranial nerve (cranial nerve X). Vagus comes from the Latin word for “wandering.” As the name suggests, the vagus goes to several places inside the

chest, abdomen, and pelvis, and it supplies the heart, lungs, and gastrointestinal tract.



The vagus nerve

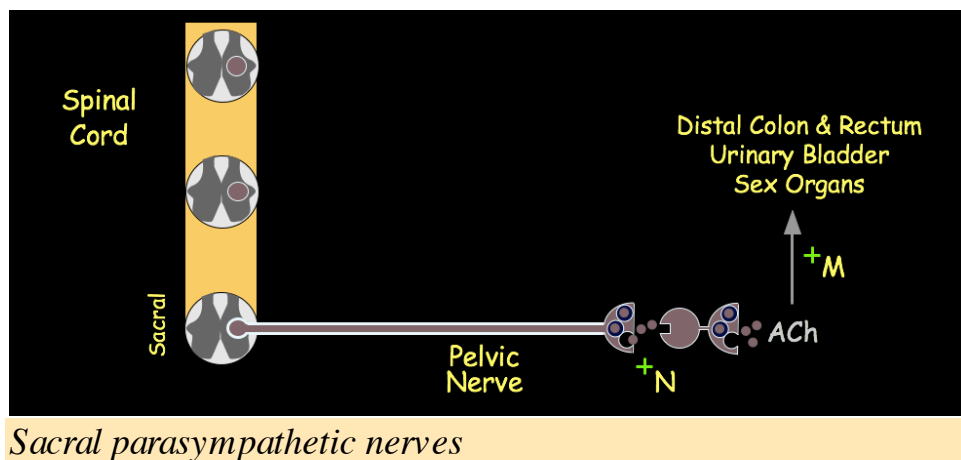
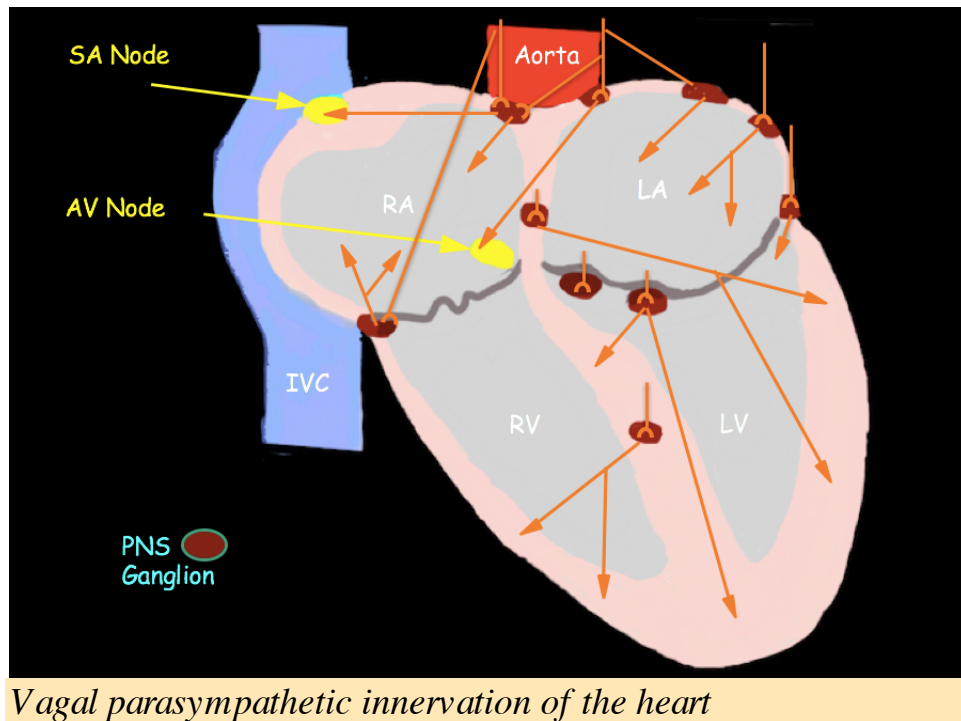
Stimulation of the vagus nerve decreases the heart rate, increases smooth muscle tone and mucus secretion in the airways, and increases secretion of stomach acid and digestive hormones.

Vagal stimulation also decreases the force of cardiac contraction (in contrast with older teaching). This occurs by at least two mechanisms. First, there are parasympathetic ganglia embedded in the myocardium, and vagal stimulation inhibits contraction of myocardial cells. Second, vagal stimulation augments the occupation of inhibitory acetylcholine receptors on sympathetic noradrenergic nerves in the myocardium.

The vagus nerve carries afferent traffic to the brain, such as from baroreceptors in the wall of the aorta. Most of the nerve fibers in the vagus actually are afferents.

The lower part of the parasympathetic nervous system are nerves from the bottom level of the spinal cord, the sacral

spinal cord. These nerves travel to the lower gastrointestinal tract, urinary bladder, and genital organs.



Sacral parasympathetic stimulation increases peristalsis in the colon and contraction of the rectum while relaxing the anal

sphincter, so that defecation occurs. Such stimulation also increases peristalsis in the ureters and activates the detrusor muscle of the urinary bladder while relaxing the urethral sphincter, so that urination occurs. Parasympathetic stimulation augments filling of the corpora cavernosum and corpus spongiosum of the penis with blood and thereby promotes penile erection.

Interference with sacral parasympathetic outflows manifests with constipation, urinary retention, and erectile dysfunction in men.

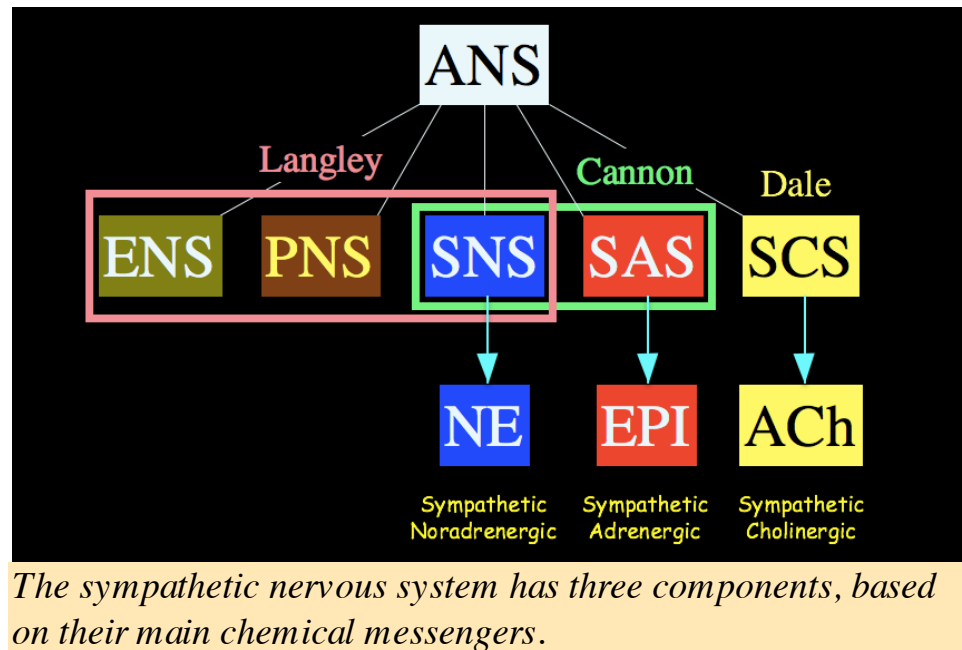
Parasympathetic nervous system failure produces many symptoms, including dry mouth, constipation, urinary problems, decreased tear production, and (in men) inability to have an erection.

THREE ROUTES TO SYMPATHY

The sympathetic nervous system is involved with processes that happen during the day or out in the open.

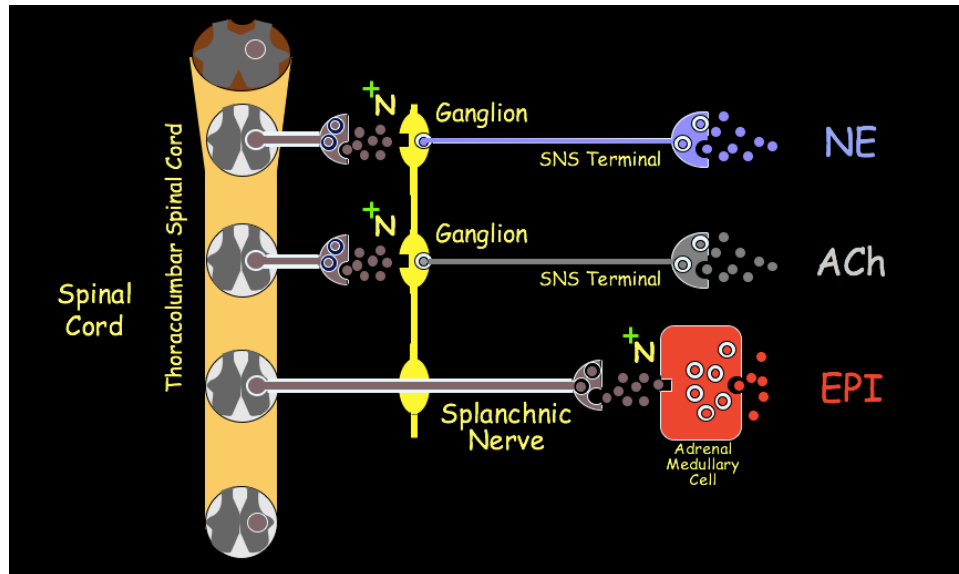
The nerves of the sympathetic nervous system come from the spinal cord at the levels of the chest and upper abdomen (thoracolumbar spinal cord). The sympathetic nerves to most organs are post-ganglionic, coming from cell bodies in the ganglia, the clusters of nerve cells like a transformer on the utility pole that supplies the electricity to your house.

The sympathetic nervous system can be thought of as being composed of three sub-systems, the sympathetic noradrenergic



system (SNS), the sympathetic cholinergic system (SCS), and the sympathetic adrenergic system (SAS), or adrenomedullary hormonal system.

These sub-systems use three different chemical messengers, norepinephrine, acetylcholine, and adrenaline. (To avoid confusion, from here on in this book, the abbreviation, SNS, is used to refer specifically to the sympathetic noradrenergic system, for which norepinephrine is the main chemical messenger.)



Organization of the 3 components of the sympathetic nervous system based on the chemical messenger— norepinephrine (NE), acetylcholine (ACh), or epinephrine (EPI).

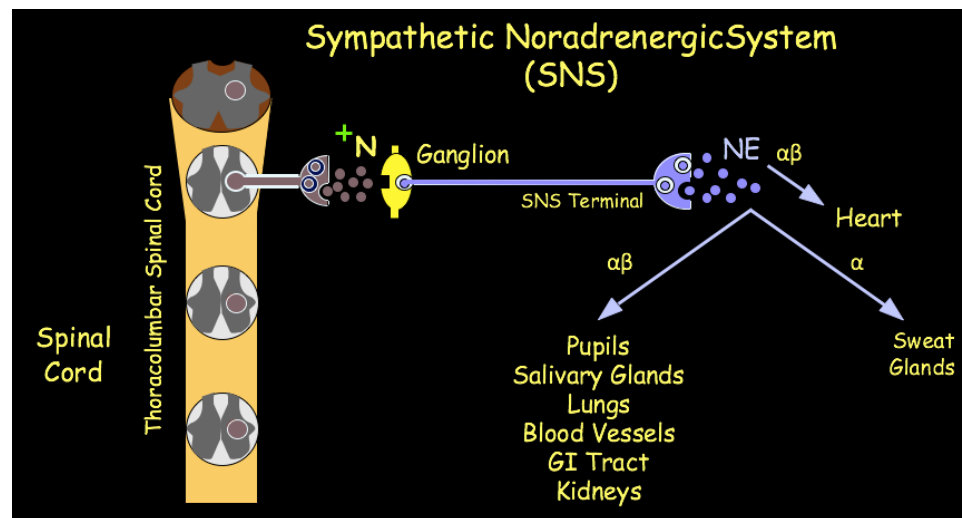
It was long thought that the sympathetic nervous system is an “emergency system” and is inactive during day to day life. Actually, this system is always active and participates in many automatic reactions that occur continually, such as tightening of blood vessels in the muscles when you stand up, keeping your glucose level within bounds if you skip a meal, and sweating when you are exposed to a warm environment.

The Sympathetic Noradrenergic System (SNS)

The sympathetic noradrenergic system consists mainly of thin,

slow-conducting, non-myelinated, post-ganglionic nerves. The neurotransmitter mediating the ganglionic transmission is acetylcholine acting at nicotinic receptors, and the neurotransmitter released from the post-ganglionic nerve terminals is norepinephrine.

Stimulation of the sympathetic noradrenergic system causes the pupils to dilate and the salivary glands to secrete thick saliva. The force and rate of the heartbeat increase. Smooth muscle cells in the airways relax. The hair stands up, because of stimulation of arrector pili muscles in the skin. In the kidneys, norepinephrine promotes tubular reabsorption of sodium.



The sympathetic noradrenergic system (SNS)

Probably the most prominent effect of sympathetic noradrenergic stimulation is constriction of blood vessels — especially of arterioles, which are the main determinant of total peripheral resistance to blood flow in the body. Decreased blood flow to the skin causes pallor. Blood flow is also decreased to the gut, skeletal muscles, and kidneys, and so the

blood pressure increases. Blood flow to vital organs—the heart, lungs, and brain—is generally preserved.

Norepinephrine exerts these effects mainly by stimulating alpha-adrenoceptors. It also is an agonist at beta-1 adrenoceptors, but, unlike adrenaline, norepinephrine is a relatively poor agonist at beta-2 adrenoceptors.

Norepinephrine is a neurotransmitter, not a hormone. Its effects in the body are determined mainly by it reaching adrenoceptors before it reaches the bloodstream.

The Sympathetic Adrenergic System (SAS)

The Sympathetic Adrenergic System (abbreviated as SAS), or Adrenomedullary Hormonal System, is the part of the sympathetic nervous system for which adrenaline is the main chemical messenger.

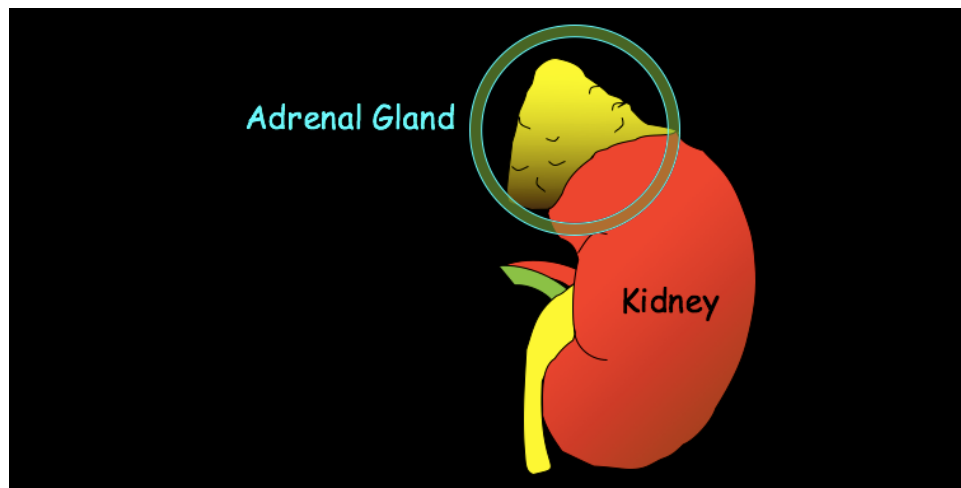
The sympathetic adrenergic system regulates “emergency” processes such as in distress. Threats to survival increase adrenaline levels.

The sympathetic adrenergic system plays a major role in responses to perceived or anticipated threats to overall homeostasis, such as lack of essential fuels (glucose and oxygen), inadequate blood flow to vital organs, and hostile encounters.

The location of the adrenal glands explains the origins of the word, adrenaline, from the Latin words for “near the kidney,”

and of the word, epinephrine, from the Greek words for “on the kidney.”

In the sympathetic adrenergic system, the connection from the spinal cord to the adrenal medullary cells is direct, and so the adrenal medulla receives rapidly conducting, myelinated fibers. This fits teleologically with the notion of adrenaline being released in sudden emergencies.

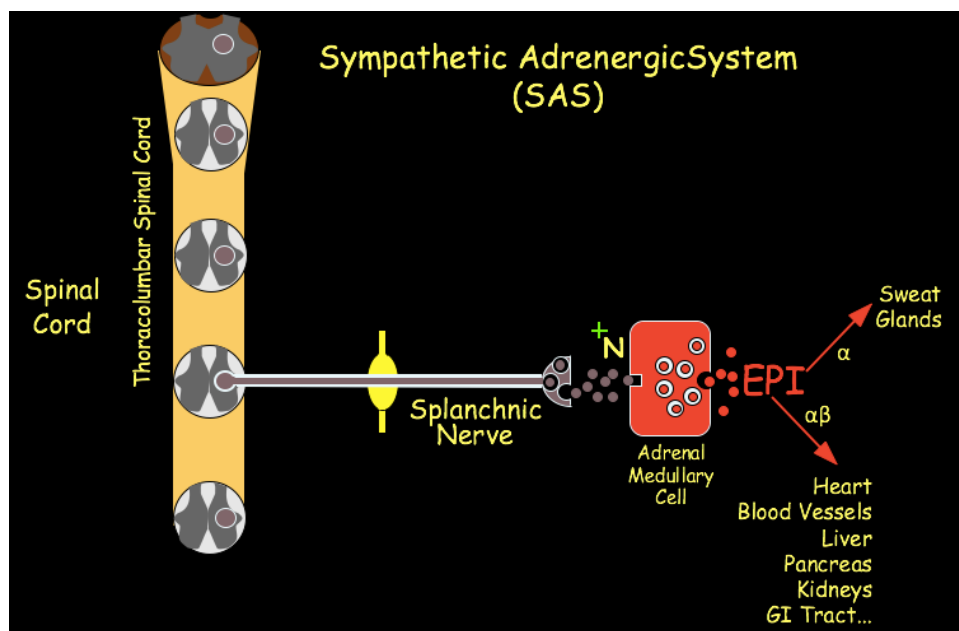


The adrenal glands are located in the fat above the kidneys. (The actual size of an adrenal gland is much smaller than drawn here.)

Adrenaline (epinephrine) is released from the adrenal glands, which sit near the tops of the kidneys.

Adrenaline is secreted into the bloodstream and is distributed widely in the body, so it is a hormone. This means that the SAS is a neuroendocrine system. Norepinephrine and acetylcholine are neurotransmitters, in that they are released from nerve terminals and act locally.

Adrenaline stimulates all types of adrenoceptors. Because of stimulation of beta-2 adrenoceptors on vascular smooth muscle cells, adrenaline increases blood flow to skeletal muscle, and probably the systemic cardiovascular effect that occurs at the lowest concentration is a fall in total peripheral resistance. At higher concentrations, adrenaline produces well known stimulation of the heart, increasing both the rate and force of contraction, and constricts blood vessels by stimulating alpha-adrenoceptors. Adrenaline also causes pallor, relaxes the gut, increases sweating, increases glucose levels, and increases the core temperature.



In the sympathetic adrenergic system (SAS), the adrenaline-secreting cells of the adrenal medulla receive direct innervation.

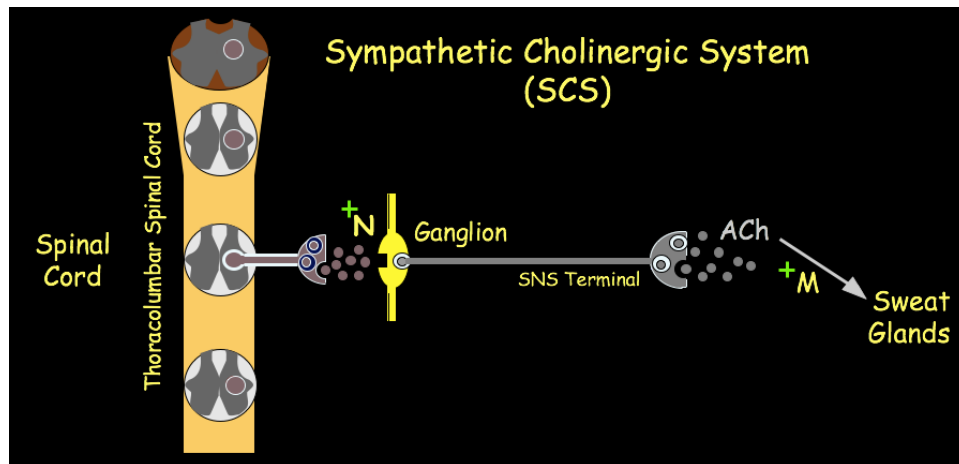
Failure of the sympathetic adrenergic system might cause a tendency to low glucose levels (hypoglycemia).

Because of adrenal blood flowing from the cortex through the

medulla, the adrenal medulla is bathed continuously in high concentrations of cortisol, the main steroid of the adrenal cortex. This is important, because cortisol is a trophic factor for PNMT, the enzyme that converts norepinephrine to adrenaline.

The Sympathetic Cholinergic System (SCS)

The sympathetic cholinergic system (abbreviated as SCS) mediates sweating—especially thermoregulatory sweating, when you perspire upon exposure to heat. The SCS also participates importantly in gustatory sweating, when you sweat on your forehead after you eat spicy foods, and in emotional sweating, when your palms and armpits sweat during distress.



The sympathetic cholinergic system consists mainly of non-myelinated post-ganglionic nerves to sweat glands.

Acetylcholine, the neurotransmitter of the sympathetic cholinergic system, stimulates secretion from sweat glands via muscarinic receptors. The sweat glands also possess adrenoceptors, which when occupied by the neurotransmitter

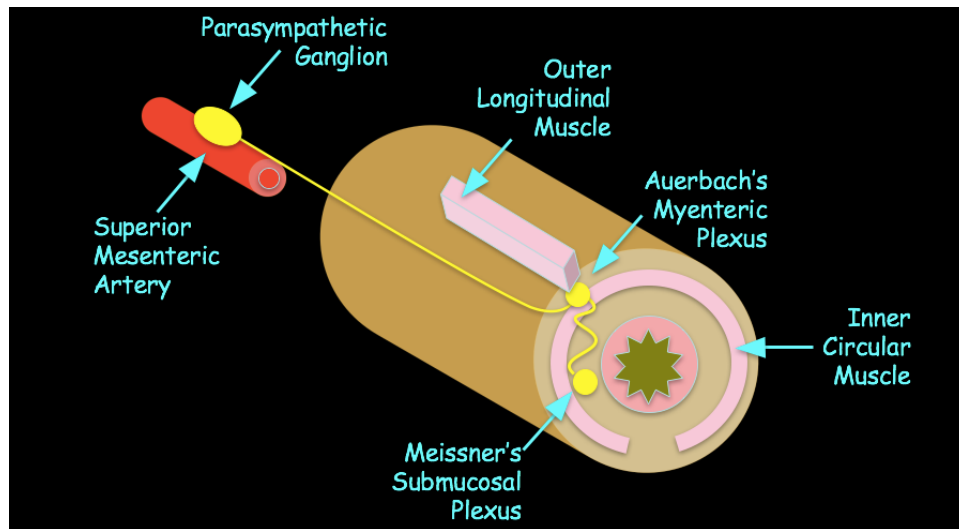
norepinephrine or the hormone adrenaline also evokes sweating.

Eccrine sweat glands (from the Greek word for “secrete”), which are the major sweat glands in the human body, occur at highest density in the palms, soles, and head. They secrete watery, salty, odorless sweat and are the main mediators of thermoregulatory sweating. Apocrine sweat glands (from the Greek words for “separate” and “away”), release sweat near hair follicles and occur at high density in the armpits, groin, and peri-anal area, as well as in the nostrils, ear canals, and areolae of the nipples. Apocrine sweat glands secrete oily, opaque sweat; its characteristic odor results from metabolic breakdown by local bacteria. This is the type of sweating associated with severe exercise and strong emotions.

THE ENTERIC NERVOUS SYSTEM (ENS)

The enteric nervous system is the part of the autonomic nervous system found within walls of the gastrointestinal tract, in plexuses (networks).

Auerbach’s plexus (also called the myenteric plexus) is between the longitudinal and circular layers of smooth muscle, and Meissner’s plexus, which is derived from fibers coming from Auerbach’s plexus, is in the submucosal layer. Auerbach’s plexus receives parasympathetic and sympathetic innervation. Meissner’s plexus receives purely parasympathetic innervation.



Arrangement of myenteric and submucosal plexuses of the enteric nervous system

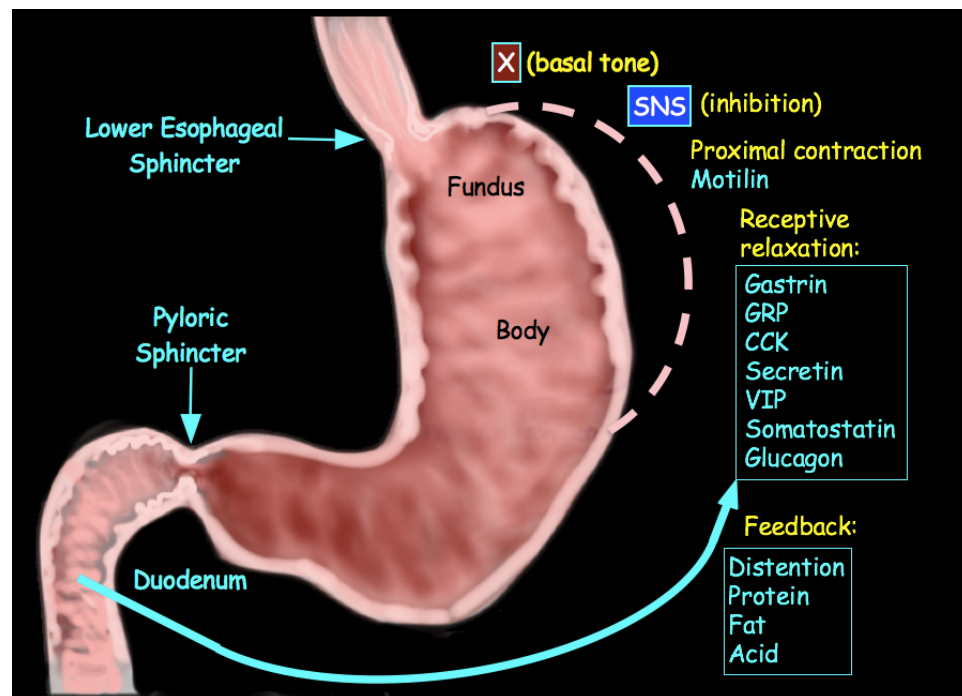
The intrinsic neurons of the ENS (ganglion cells) migrate from the neural crest during fetal development. The ganglion cells are required for movement of intestinal contents.

In Hirschsprung's disease this migration is incomplete, and the affected segment of the colon that lacks the ganglion cells cannot relax and move stool through the colon. Hirschsprung's disease therefore manifests clinically with failure of the newborn to pass meconium or stool.

The ENS contains many neurotransmitters. It is difficult if not impossible to assess the ENS specifically by physiological tests, because gastrointestinal functions are regulated importantly by extrinsic parasympathetic and sympathetic nerves, hormones, autocrine/paracrine factors, and local effects such as from

distention.

It is a surprising fact that most of the norepinephrine, dopamine, and serotonin made in the body is synthesized and metabolized in the gut.



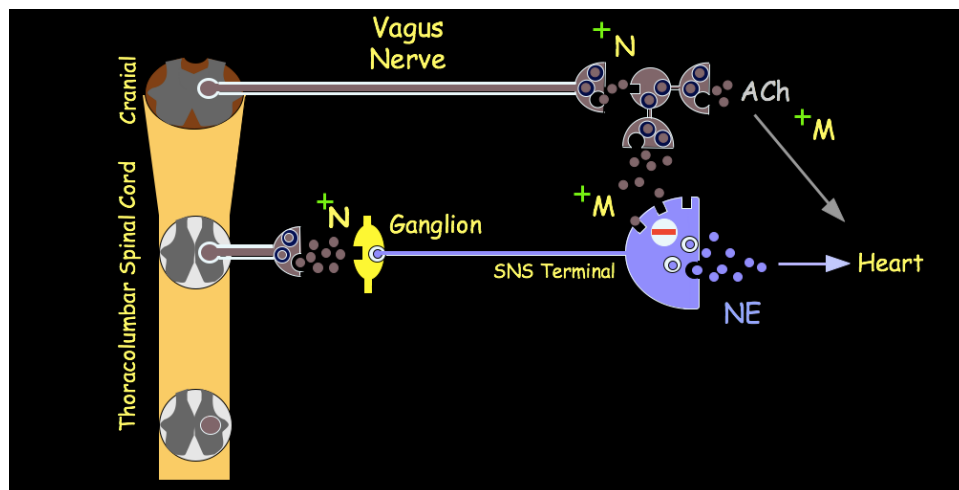
Autonomic regulation of the stomach involves a complex combination of extrinsic innervation, hormones, autocrine/paracrine factors, and local feedback.

Interactions among ANS Components

Activation of particular components of the autonomic nervous system can lead to effects on other components. That is, the components interact with each other.

For instance, the sympathetic noradrenergic system and the

parasympathetic nervous system usually antagonize each other. When sympathetic nerves in the heart are stimulated, the heart rate speeds up, and the heart beats more forcefully, whereas when parasympathetic nerves in the heart are stimulated, the heart rate slows down, and the heart beats less forcefully. There are inhibitory muscarinic receptors on sympathetic post-ganglionic nerves in the heart. Because of this, vagal stimulation decreases the rate and force of cardiac contraction, not only directly by the released acetylcholine acting at muscarinic receptors on the target myocardial cells but also indirectly by inhibiting norepinephrine release from sympathetic post-ganglionic nerves.

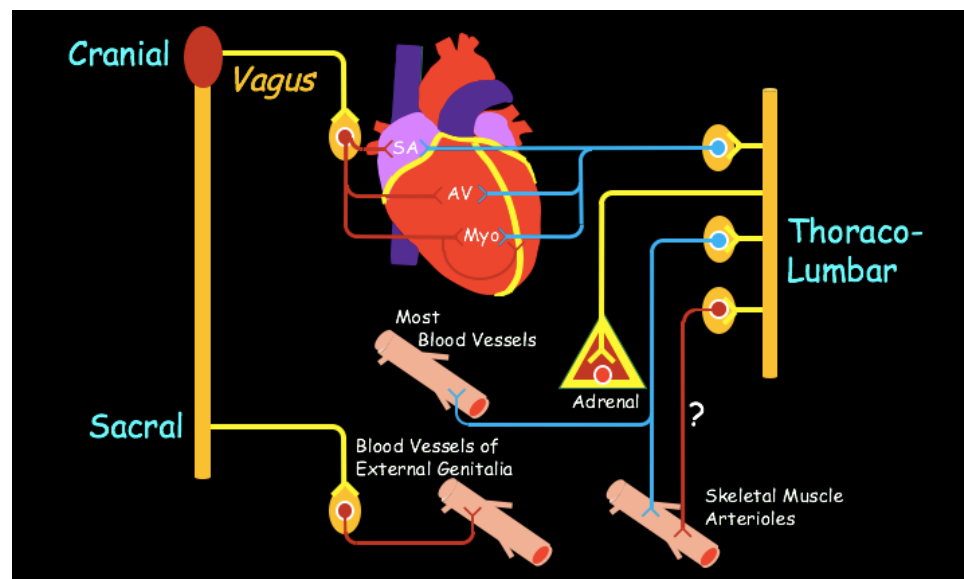


Components of the autonomic nervous system can interact. For instance, acetylcholine (ACh) released from vagal terminals can inhibit norepinephrine (NE) release from sympathetic noradrenergic system (SNS) terminals.

In some forms of dysautonomia, multiple components of the autonomic nervous system are affected similarly. For instance, interference with the transmission of nerve impulses in the ganglia produces symptoms and signs of failure of the

sympathetic noradrenergic system, the sympathetic cholinergic system, the sympathetic adrenergic system, and the parasympathetic nervous system.

The sympathetic noradrenergic system and the parasympathetic nervous system usually antagonize each other...but not always.



Overview of autonomic regulation of the cardiovascular system

In other situations, increases in activities of these systems go together. An example is after eating a meal. In this setting, stimulation of the parasympathetic nervous system aids digestion, by increasing gut motions and augmenting secretion of hormones such as insulin. Meanwhile, stimulation of the sympathetic noradrenergic system tightens blood vessels in particular body regions, shunting blood toward the gut. After a meal, possibly because of increased levels of glucose in the bloodstream, activity of the sympathetic adrenergic system

tends to decrease.

Fainting involves a complex and unusual pattern of changes in activities of components of the autonomic nervous system. When people faint, activity of the parasympathetic nervous system usually is increased, producing changes such as nausea, churning stomach, and a prominent fall in the heart rate. Activity of the sympathetic noradrenergic system often is decreased, resulting in a fall in blood pressure. The sympathetic adrenergic system is stimulated markedly, and high levels of adrenaline in the bloodstream are probably responsible for constriction of blood vessels in the skin, resulting in pallor and dilation of the pupils. Finally, when people faint they often have increased sweating, reflecting either increased activity of the sympathetic cholinergic system or effects of high circulating adrenaline levels.

It has been taught that the sympathetic noradrenergic system and the adrenomedullary hormonal system act together in emergencies such as “fight-or-flight” situations. Automatic adjustments to stresses of everyday life, such as standing up or going outside on a chilly day, also involve increases in activities of both systems (although mainly of the sympathetic noradrenergic system). As noted above, in fainting activities of some components of the autonomic nervous system change in opposite directions.

Stimulation of the sympathetic noradrenergic system tightens blood vessels and increases the force of the heartbeat (the combination increasing blood pressure), relaxes the gut, evokes goose bumps, the hair standing out, and sweating, promotes retention of sodium by the kidneys, increases production of

thick saliva, and dilates the pupils. Stimulation of the sympathetic cholinergic system evokes sweating. Stimulation of the enteric nervous system increases gut motions. Stimulation of the sympathetic adrenergic system increases the rate and force of the heartbeat, tightens blood vessels in the skin (producing pallor), relaxes blood vessels in skeletal muscle, relaxes the gut, increases blood glucose levels, decreases serum potassium levels, contributes to emotional sweating, exerts an anti-fatigue effect, and intensifies emotional experiences.

	SNS	SAS
2-Deoxyglucose (glucoprivic stress)	+	++++
Distress	+	+++
Autonomically mediated syncope (fainting)	+	++++
Orthostasis	++	+
Mild exercise	++	+
Cool temperature at skin of back	+++	0
Mild core hypothermia	+++	+

Some situations where there is differential activation of the SNS vs. the SAS

The sympathetic noradrenergic system (norepinephrine the chemical messenger) and the sympathetic adrenergic system (adrenaline the chemical messenger) usually work together...but not always.

Stimulation of the parasympathetic nervous system decreases the heart rate, increases production of watery saliva, stimulates the gut, stimulates the urinary bladder, promotes erection of the penis, and constricts the pupils of the eyes.

Given the many different effects of stimulation of components of the autonomic nervous system, you may begin to predict what the symptoms and signs would be when those components are overactive or underactive in dysautonomias.

Activation of the different components of the autonomic nervous system produces different effects on the body.

Sweating and blood pressure are “automatic” functions controlled by different chemicals.

The ganglion cells of the ENS contain many putative chemical messengers, including acetylcholine, serotonin, and dopamine. How the ganglion cells with their multiple neurotransmitters interact with the parasympathetic nervous and sympathetic noradrenergic systems remains incompletely understood.

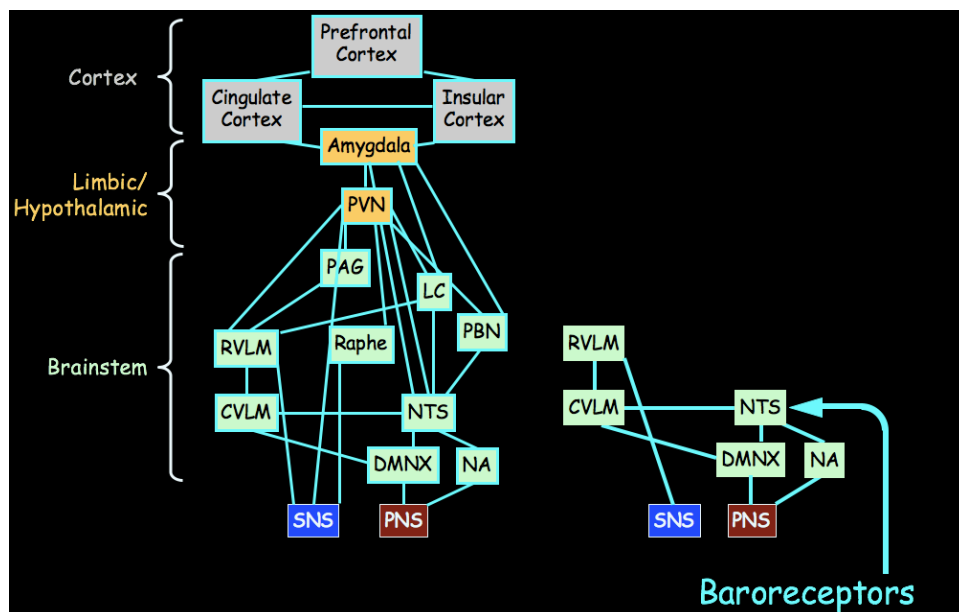
The Central Autonomic Network

Several cortical, subcortical, and brainstem centers in a network participate in regulation of outflows to the autonomic nervous system. This has been called the “central autonomic network.”

Cortical centers include the prefrontal cortex, anterior cingulate cortex, and insular cortex. Subcortical centers include the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus.

Brainstem centers include the peri-aqueductal gray region in the

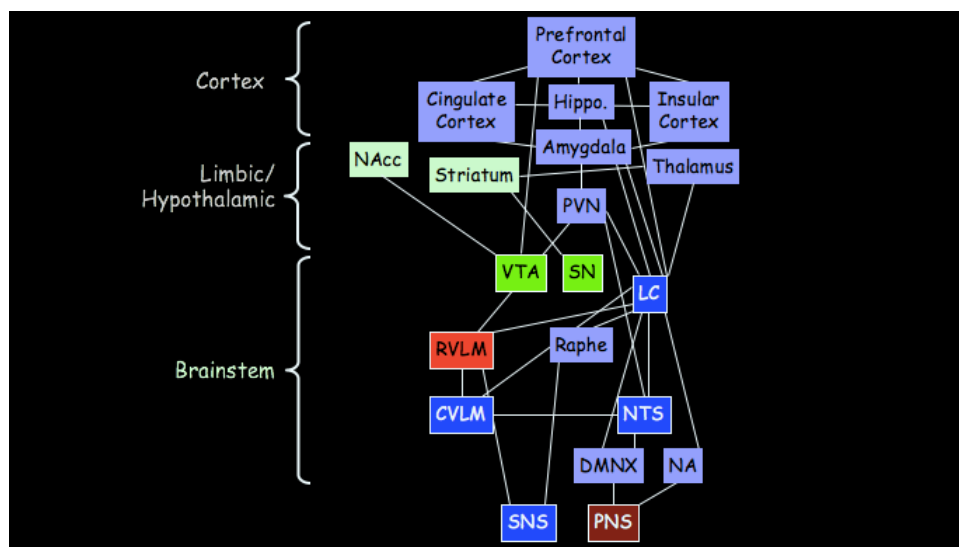
midbrain, the parabrachial nucleus at the junction of the midbrain and pons, the locus ceruleus in the dorsal pons, and the raphe nuclei, rostral ventrolateral medulla, caudal ventrolateral medulla, dorsal motor nucleus of the vagus, nucleus ambiguus, and nucleus of the solitary tract in the medulla.



The central autonomic network involves complex interconnections among clusters of neurons at different levels of the neuraxis. Pathways involved in the baroreflex are shown in the portion in the lower right.

The central autonomic network is organized not only in neuroanatomic terms but also in neurochemical terms and includes systems for each of the body's three catecholamines. The locus ceruleus in the pons supplies noradrenergic fibers to most higher centers in the brain (an exception is the hypothalamus, which receives noradrenergic fibers from medullary noradrenergic neurons). Dopaminergic fibers in the

brain emanate mainly from the substantia nigra and ventral tegmental area in the midbrain. The nigral neurons richly innervate the striatum (caudate and putamen), and the nigrostriatal system is important in initiation of movement. The ventral tegmental neurons innervate the nucleus accumbens, and the nucleus accumbens is important for motivation, pleasure, reward, and reinforcement learning and therefore in addiction.



A central neurochemical network involves the catecholamines norepinephrine (blue), epinephrine (red), and dopamine (green).

Epinephrine-synthesizing neurons in the rostral ventrolateral medulla project in the intermediolateral columns of the spinal cord to the sympathetic pre-ganglionic neurons.

In most of the brain epinephrine is not normally detected. It is possible that in distressing situations evoking substantial adrenomedullary secretion, epinephrine can increase blood pressure and thereby interfere with its own blood-brain barrier and enter the brain.

Summary of the Organization of the ANS

Now is a good time for us to review the information so far. It can be a bit confusing, because of the several “nervous systems” involved.

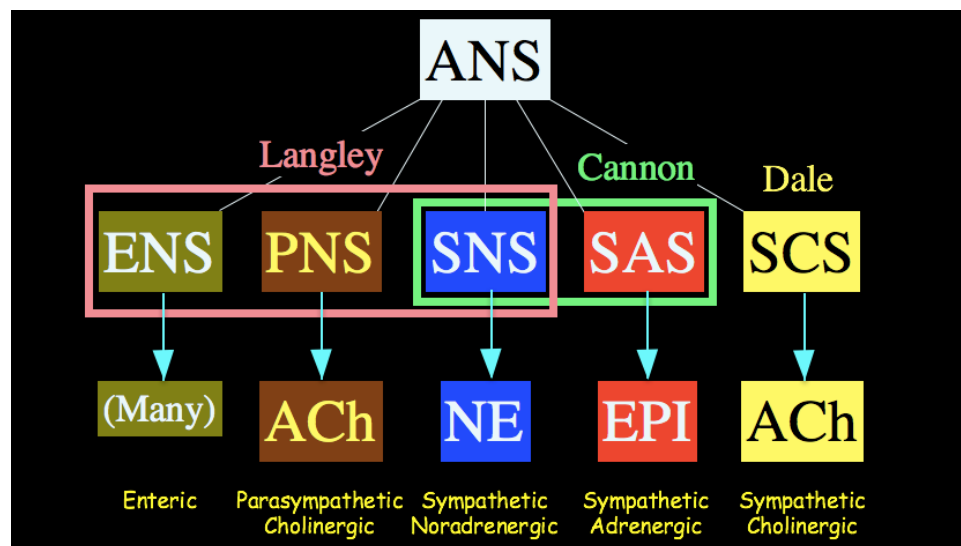
Remember, you have a central nervous system (your brain and spinal cord) and a peripheral nervous system (the rest of your nerves). Your peripheral nervous system has two divisions, the somatic nervous system and the autonomic nervous system. The somatic nervous system is concerned with the “outer world,” and the nerves in this system travel to skeletal muscle. Your autonomic nervous system is concerned with the “inner world” within the body, and it usually works automatically, so that you can think of the autonomic nervous system as the “automatic nervous system.”

The control signals of the autonomic nervous system travel indirectly from your central nervous system through ganglia (clusters of nerve cells) to smooth muscle, found in areas like your blood vessels, heart, and glands throughout the body. Nerves coming to the ganglia from the spinal cord are pre-ganglionic. Nerves coming from the ganglia are post-ganglionic. Some nerves, such as those to the adrenal glands, pass through the ganglia without relaying within the ganglia, so that there is a direct connection from the central nervous system to the target organs.

You have also learned that there are several components of the autonomic nervous system. Two of the main components are the sympathetic nervous system and the parasympathetic nervous system.

The sympathetic nervous system can in turn be divided into sub-systems based on the chemical messenger use for that component—norepinephrine for the sympathetic noradrenergic system, acetylcholine for the sympathetic cholinergic system, and adrenaline for the sympathetic adrenergic system.

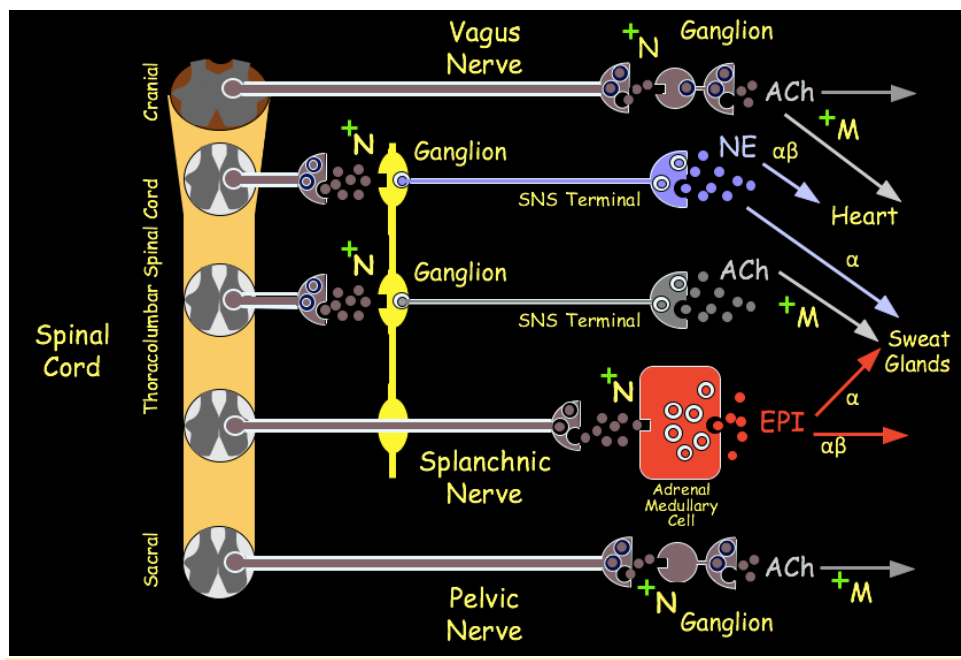
You have also learned that the autonomic nervous system works by releasing chemical messengers, which act on receptors located in organs throughout the body. Chemical messengers coming from nerves are neurotransmitters, and chemical messengers released into the bloodstream are hormones.



Five components of the ANS.

The adrenal glands, located near the tops of the kidneys, are the source of the hormone adrenaline. The combination of the

adrenal medulla with the sympathetic nervous system has been called the “sympathoadrenal system,” which has been thought to function as a unit in emergencies such as “fight-or-flight” situations. Sometimes components of the autonomic nervous system work together, sometimes they antagonize each other, and sometimes changes activities of the different components occur in characteristic patterns.



Overview of the distribution of autonomic nerves

Finally, you have learned about the distribution of autonomic nerves in the body. Parasympathetic nerves come from the brainstem and sacral spinal cord, and sympathetic nerves (noradrenergic, adrenergic, and cholinergic) come from the thoracolumbar spinal cord. Parasympathetic nerves have long, myelinated pre-ganglionic and short, non-myelinated post-ganglionic fibers. Sympathetic noradrenergic and cholinergic nerves have short, myelinated pre-ganglionic fibers and long,

non-myelinated post-ganglionic fibers. Sympathetic adrenergic nerves going to the adrenal medulla are myelinated fibers, but instead of post-ganglionic nerves the adrenal cells secrete adrenaline into the bloodstream.

HOW DOES THE ANS WORK?

GETTING THE MESSAGE ACROSS

Chemical Messengers of the ANS: An Introduction

The autonomic nervous system works by releasing messenger chemicals inside the body. These chemicals act on receptors on target cells, such as heart muscle cells, and this changes body functions.

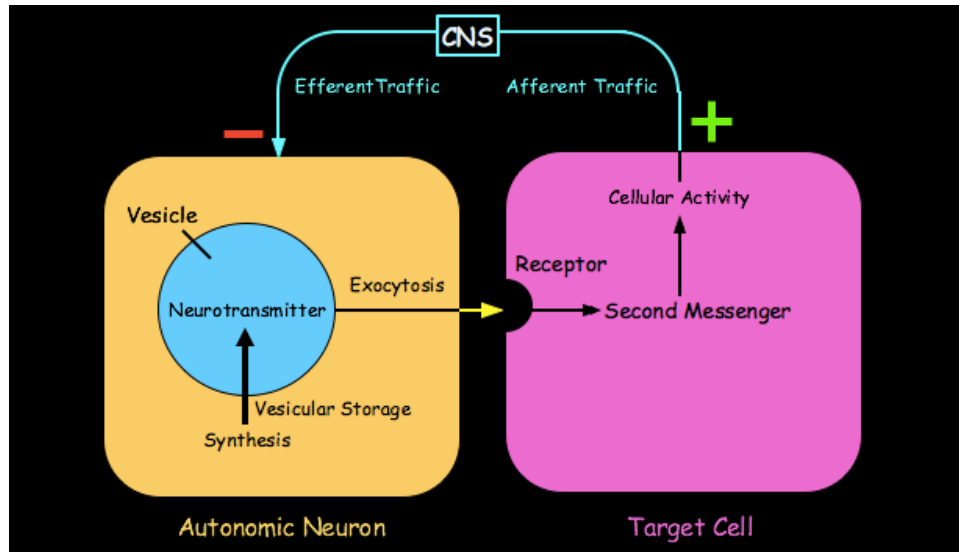
The main chemical messengers of the autonomic nervous system are the neurotransmitters, acetylcholine and norepinephrine, and the hormone, adrenaline.

Acetylcholine is the chemical messenger of the parasympathetic nervous system (PNS), the sympathetic cholinergic system (SCS), and the somatic nervous system. Norepinephrine is the chemical messenger of the sympathetic noradrenergic system (SNS), and adrenaline is the chemical messenger of the sympathetic adrenergic system (SAS).

The transmission of chemicals in the autonomic nervous system (neurotransmission) involves some common steps, although there are variations on the theme.

Acetylcholine, norepinephrine, and adrenaline are stored in tiny

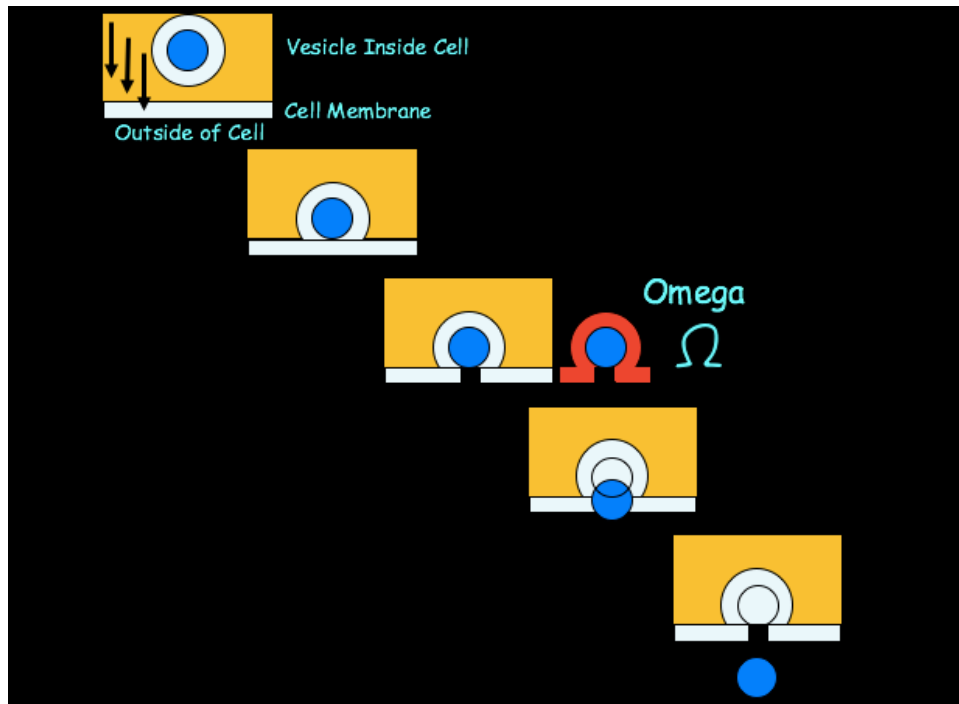
bubble-like structures called vesicles. Acetylcholine and adrenaline are produced in the cytoplasm (“cell juice”) and then are actively pumped into the vesicles. Norepinephrine is produced within the vesicles.



Some common themes in how autonomic nerves work.

The neurotransmitter is released by a process called exocytosis, where the vesicle moves to the membrane surface of the cell, a hole forms at the junction of the vesicle with the cell membrane (microscopically, there is a little “omega sign”), and the messenger makes its way out of the cell.

Neurotransmitters and hormones sometimes are called “first messengers.” They reach specific proteins, receptors, on the target cells. For instance, acetylcholine released from parasympathetic nerves in the heart binds to cholinergic receptors, and this causes the heart rate to decrease.



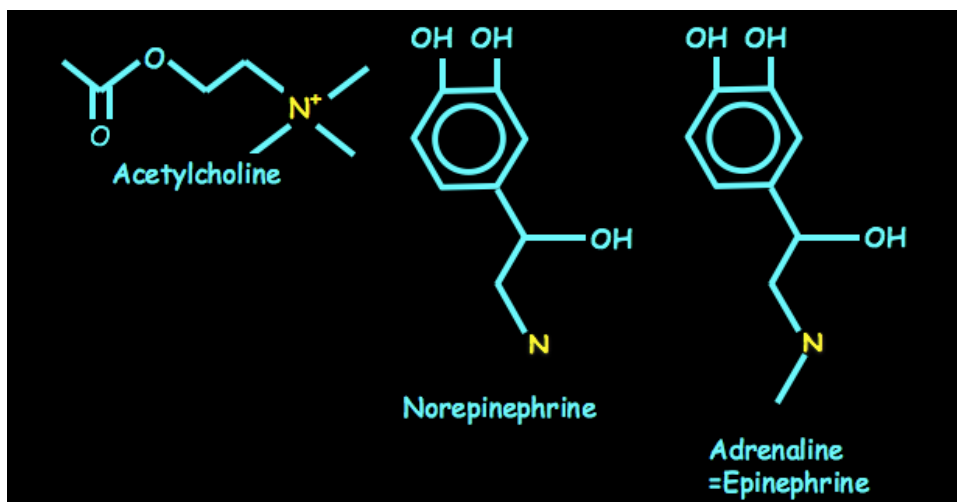
Exocytosis, the process of neurotransmitter release

Occupation of the receptors leads to alterations in levels or activity of “second messengers” in the target cells. It is the second messengers that actually change the functional state of the cells.

Finally, activation or inhibition of the state of activity of the target cells alters information traveling to the central nervous system. Reflexive changes in traffic in the autonomic nerves complete a negative feedback loop. Because of the negative feedback loop, the level of an internal variable is kept within bounds. For example, when you exercise on a hot day, your core temperature tends to increase. Activation of a part of the autonomic nervous system (the sympathetic cholinergic system) releases the neurotransmitter acetylcholine from terminals of nerves supplying sweat glands, activating receptors on the cells

of the sweat glands. A cascade of intra-cellular events occurs that evokes sweat by the glands. This increases evaporative heat loss, which keeps the core temperature within bounds. This negative feedback loop is so rapid and efficient, exercising in the heat normally doesn't elevate core temperature at all.

Acetylcholine, norepinephrine, and adrenaline are small molecules. They all contain a prominent, single nitrogen (N) atom—a quaternary ammonium ion in acetylcholine and an amine group in norepinephrine and adrenaline. They are basic, meaning that at a neutral pH they are positively charged. And they are actively taken up into and stored in vesicles, which

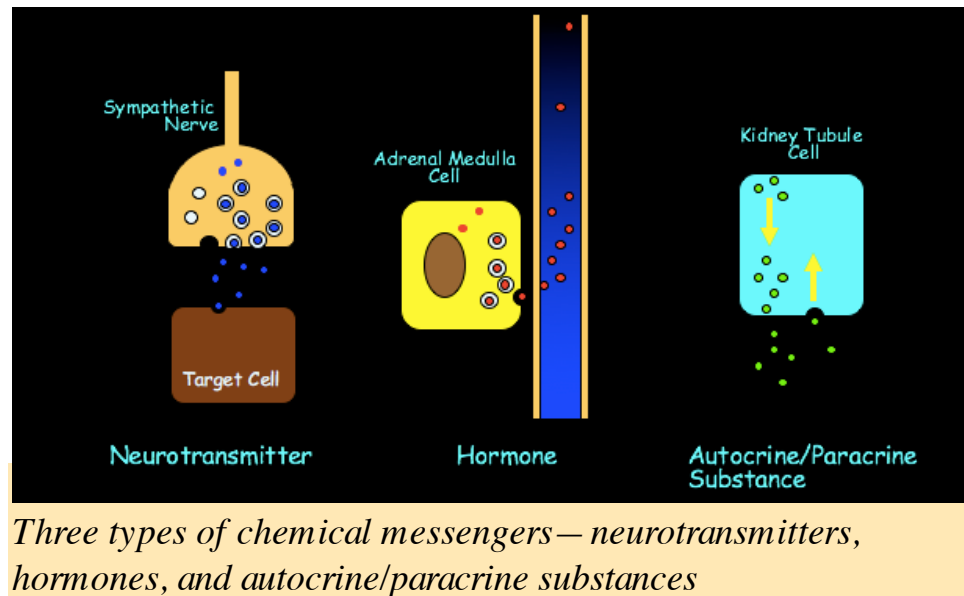


*Chemical messengers of the autonomic nervous system
acetylcholine, norepinephrine, and adrenaline (epinephrine)*

have a relatively acidic pH.

There are at least four types of chemical messengers released in your body. The first type of chemical messenger is released from nerves. Chemicals released from nerves are

neurotransmitters.



Automatic systems of the body use at least four types of chemical messenger.

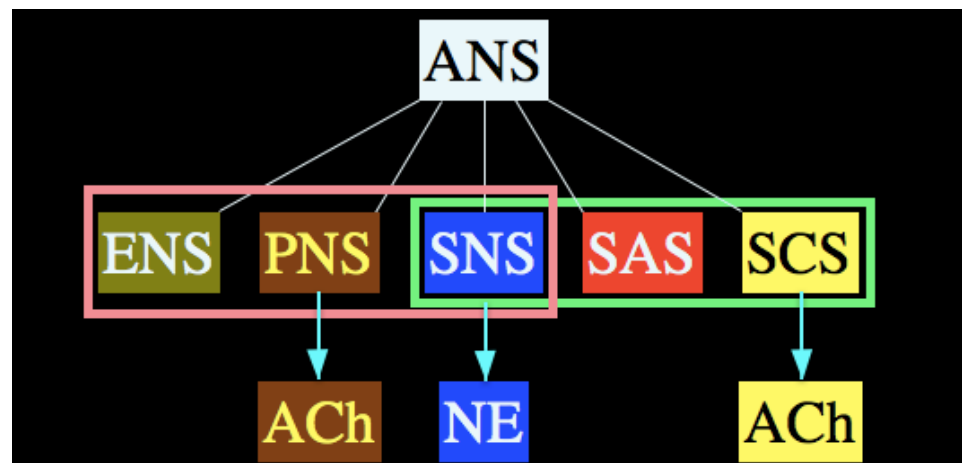
Neurotransmitters act locally and are inactivated locally. This means that only a relatively small amount of released neurotransmitter makes its way to the bloodstream unchanged.

Chemical messengers released from nerves are neurotransmitters.

Two of the main neurotransmitters of the autonomic nervous system are norepinephrine and acetylcholine. Small amounts of norepinephrine are detectable in the plasma, and measurement of plasma norepinephrine is a common test in the evaluation of

dysautonomias thought to involve the sympathetic noradrenergic system; however, because of neuronal reuptake, only a small proportion of released norepinephrine makes its way to the bloodstream unchanged.

Acetylcholine released from nerves of the parasympathetic nervous system and from nerves of the sympathetic cholinergic system is so rapidly and efficiently broken down that acetylcholine is not normally detectable in the plasma. Therefore, tests of the parasympathetic and of the sympathetic cholinergic system rely on other types of measurements.

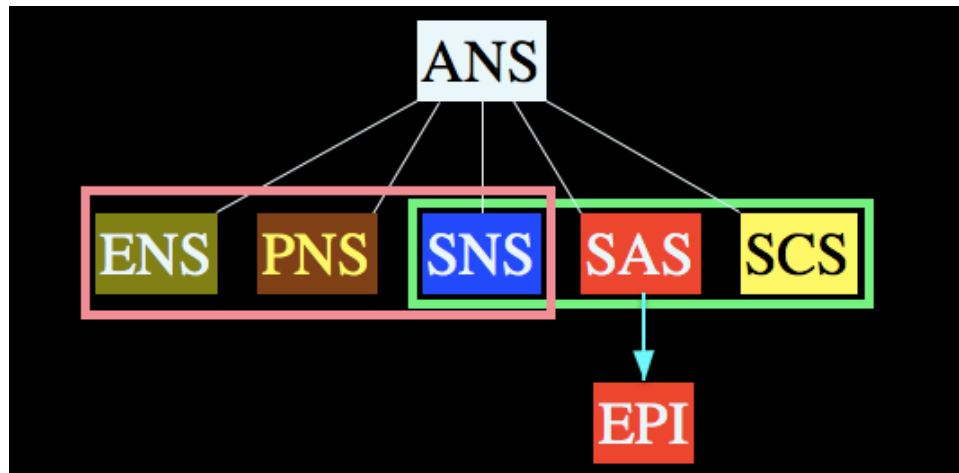


Acetylcholine and norepinephrine are the main neurotransmitters of the autonomic nervous system.

Hormones are released directly into the bloodstream and are delivered to all body organs.

One of the most famous hormones, and the first whose structure was identified, is adrenaline, which is released into the

bloodstream by the adrenal gland. Essentially all body organs take up circulating adrenaline; however, an exception is the brain, where an efficient blood-brain barrier prevents entry of catecholamines into most brain regions.

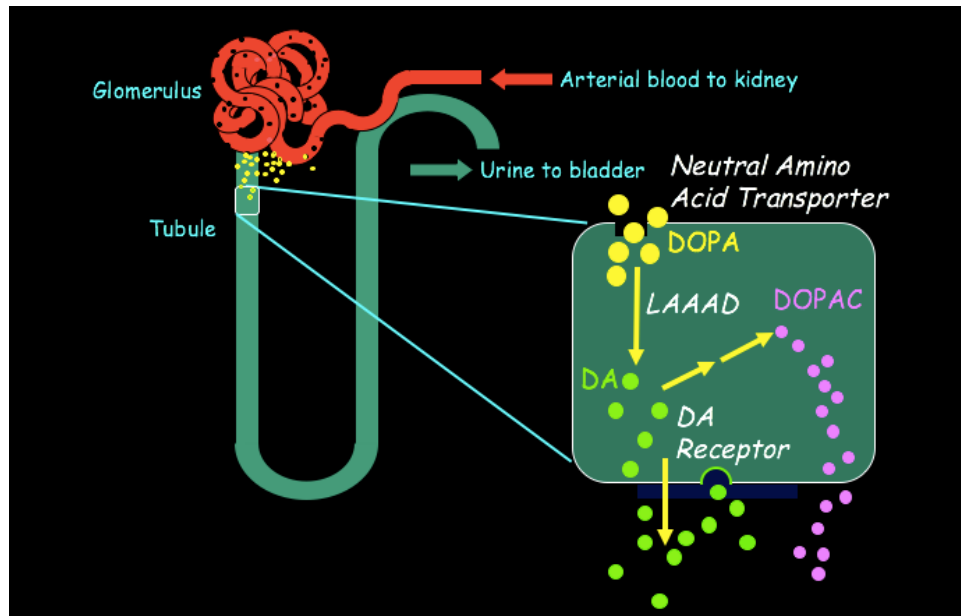


Adrenaline, or epinephrine (EPI), is the chemical messenger of the sympathetic adrenergic system (SAS). EPI is a hormone.

A third type of chemical messenger is probably old in terms of evolution but new in terms of recognition by scientists. This class of chemicals are autocrine/paracrine substances. They are made in, released from, and act on the same or nearby target cells within the tissue.

Autocrine/paracrine substances are made in, released by, and act on the same or nearby cells in an organ.

Autocrine/paracrine substances are released just about as soon as they are made within the cells, unlike hormones and neurotransmitters, which are stored at particular sites within cells and are released from the storage sites in response to nerve



The renal DOPA-dopamine autocrine/paracrine system

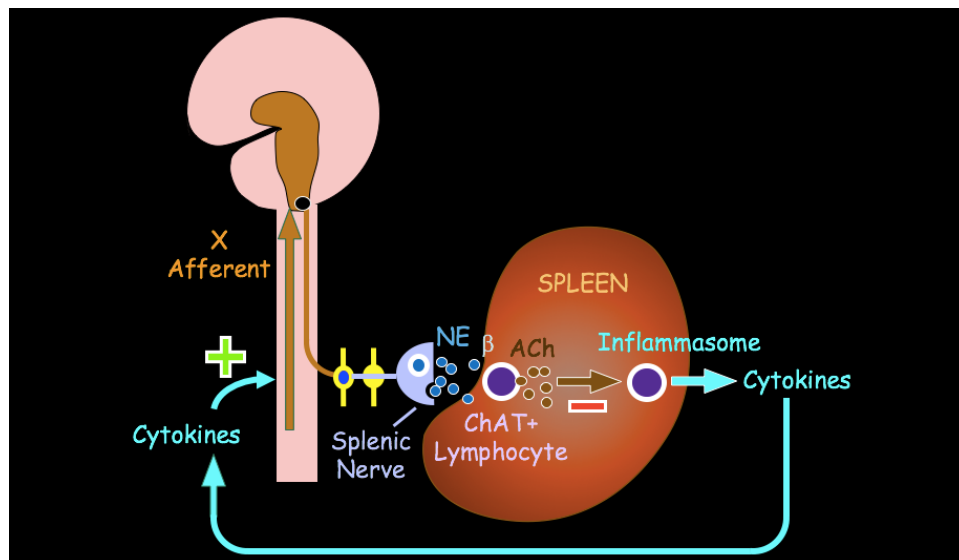
traffic.

Of several autocrine/paracrine substances in the body, one involves the catecholamine, dopamine. In proximal tubular cells of the kidneys, DOPA is converted to dopamine by the enzyme L-aromatic-amino-acid decarboxylase (LAAAD). Dopamine released from the cells acts on dopamine receptors on the same or nearby cells, and this increases excretion of sodium and water.

A large family of proteins called cytokines that are released from cells of the immune system exemplify a fourth type of chemical messenger. Cytokines play key roles in immunity and bodily responses to infection, inflammation, trauma, sepsis, and cancer.

Neuroimmunology is a rapidly evolving field that focuses on

interactions between the nervous system (including the autonomic nervous system) and immune functions (including cytokines).



A system involving the vagus nerve and cytokines regulates immune functions via a negative feedback loop.

One example of neuroimmune interactions is regulation of cytokines by the vagus nerve.

The parts of the autonomic nervous system have particular chemical messengers.

Acetylcholine released from parasympathetic nerves produces many effects in the body, including increasing the tone of the urinary bladder and bowel, increasing gastric acid secretion, stimulating salivation and tear production, and decreasing the rate and force of the heartbeat.

Acetylcholine is important for “vegetative” activities like salivating, digesting, and getting rid of waste.

Acetylcholine is also the neurotransmitter of the sympathetic cholinergic system (SCS). Acetylcholine release from sympathetic cholinergic nerves acts at sweat glands, causing perspiration. Sweating responses have been classified as thermoregulatory (such as sweating when exercising in the heat), gustatory (sweating mainly on the forehead after eating, especially chili peppers), and emotional.

Acetylcholine is also important for sweating.

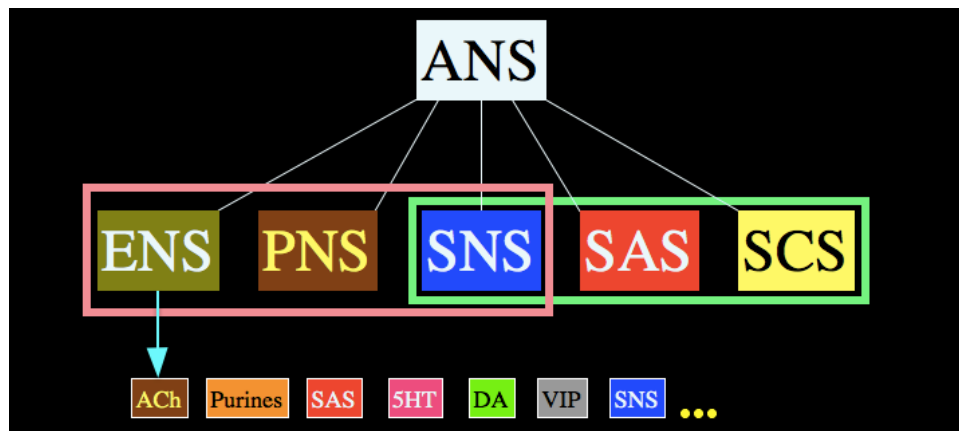
Norepinephrine (NE), the neurotransmitter of the sympathetic noradrenergic system (SNS) plays a major role in regulation of the heart and blood vessels during all activities of daily life, such as standing, walking, and after eating a meal.

Epinephrine (EPI), or adrenaline, the main chemical messenger of the sympathetic adrenergic system (SAS), helps maintain organismic integrity in response to overall challenges such as hypoglycemia, hypothermia, hemorrhagic hypotension, anoxia, and emotional distress.

EPI produces prominent cardiovascular effects. By constricting blood vessels in the skin, adrenaline produces pallor. EPI is also one of the three hormones regulating blood glucose levels (the others are insulin and glucagon) and is probably responsible for the hyperglycemia that typically attends emergencies. EPI activates platelets and thereby helps

minimize traumatic blood loss. Since EPI generates calories and constricts cutaneous blood vessels, the core temperature tends to increase. The combination of cutaneous vasoconstriction and EPI-induced sweating probably explains the “cold sweat” that typifies people in shock.

The bloodstream delivers adrenaline throughout the body.



The enteric nervous system (ENS) involves many neurotransmitters.

There is no single neurotransmitter of the enteric nervous system. Most of the serotonin and dopamine made in the body is produced in the gut. Acetylcholine is another enteric neurotransmitter, and there are many others.

The Search for the Omega Sign

Once produced in the vesicles in autonomic nerves, neurotransmitters are released from the nerve terminals by the



Thomas Renton Elliott, a student of Langley, was the first to propose the idea of chemical neurotransmission.

exocytosis process.

Exocytosis, a key element in the theory of chemical neurotransmission, was first proposed by Thomas Renton Elliott in 1904. Elliott was a student of Langley—the same Langley who coined the phrase, “autonomic nervous system.”

Elliott’s idea arose from the observation that stimulation of sympathetic nerves and injection of adrenal gland extract produce similar effects in the body. In a stroke of genius, he hypothesized that the similarity resulted from a chemical like adrenaline actually being released from the nerves and acting on nearby cells. His brief note, published in the *Journal of Physiology*, proposed “a mechanism developed out of the muscle cell, in response to its union with the synapsing sympathetic fibre, the function of which is to receive and transform the nervous impulse. Adrenalin(e) might then be a chemical stimulant liberated on each occasion when the impulse arrives at the periphery.”

It took until the early 1920s for experimental proof of this concept to emerge, and the scientist who provided that proof, Otto Loewi, received a Nobel Prize in 1936 for his discovery of the first neurotransmitter, acetylcholine. As noted elsewhere, Loewi also thought he had obtained proof that adrenaline is the neurotransmitter of the sympathetic nerves—but he actually hadn't.

According to the exocytosis theory chemical neurotransmission results from physical movement of the bubble-like vesicles containing the neurotransmitter toward the cell membrane, fusion of the vesicle membrane with the cell membrane, pore formation at the site of fusion of the two membranes, and entry of the contents of the vesicles into the fluid outside the cell. Among those contents is the neurotransmitter, which diffuses a short way to reach receptors on the membrane of the target cells.

One way to test the theory of exocytosis would be by direct visualization. If the vesicle membrane actually fused with the cell membrane and a hole formed at the junction, then if one looked under an electron microscope at the nerve terminal, one would see tiny “omega signs” or see the vesicle contents coming through the cell membrane. Recent highly sophisticated techniques have enabled such direct visualization; however, only a very small percentage of vesicles are actually found poking their way through the membrane surface.

CATECHOLS LOOK LIKE CATS

Two of the most important parts of the autonomic nervous system use members of the catecholamine family as the main chemical messengers.

Concentrations of catecholamines can be measured in body fluids such as the plasma, urine, or cerebrospinal fluid. By assaying levels of catecholamines and their breakdown products, one can gain insights into the diagnosis of patients with complaints referable to the autonomic nervous system. Later on we will be dealing in depth about the many ways clinical catecholamine neurochemistry is important for diagnosis, understanding disease mechanisms, and treatment of dysautonomias.

Measuring levels of catecholamines and related chemicals aids the workup of patients with dysautonomias.

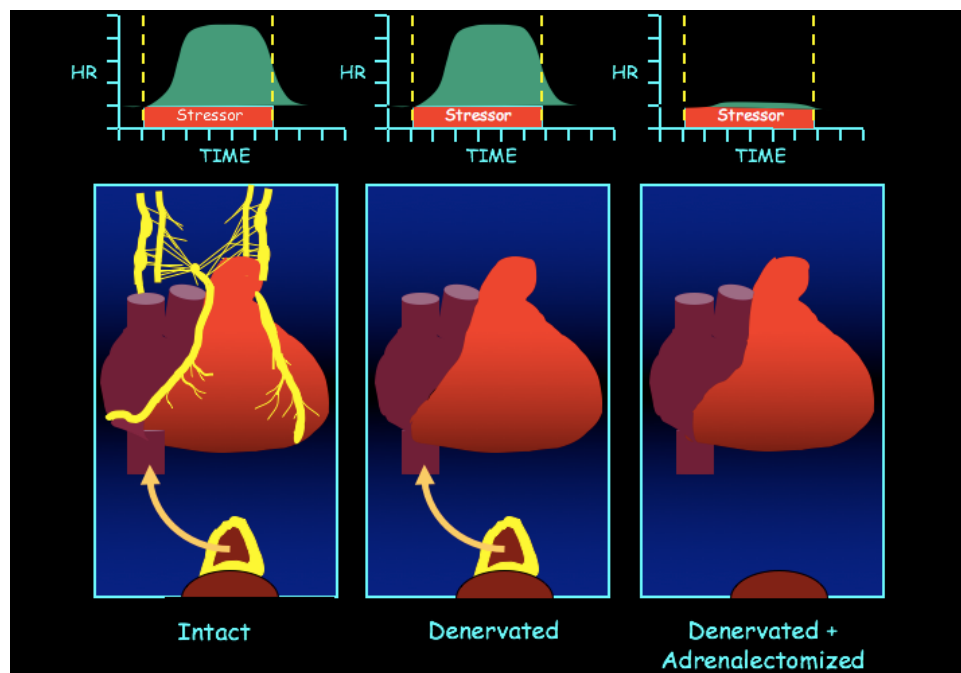
Virtually every dysautonomia and every treatment for dysautonomias involves catecholamines directly or indirectly.

In addition, drugs that affect the production, release, or inactivation of catecholamines or that work by stimulating or blocking receptors for catecholamines are commonly used in

the treatment of various forms of dysautonomia.

Cannon's Ingenious Experiment

Beginning in about 1919 and over the next two decades, Walter B. Cannon used a clever experimental setup to identify and quantify adrenaline release during stress. He would surgically excise the nerves supplying the heart of a laboratory animal such as a dog or cat. Then he would subject the animal to a stressor and record the heart rate response.



Walter B. Cannon used an ingenious denervated heart preparation to measure adrenaline release in response to different stressors.

With the nerves to the heart removed, he could conclude that if the heart rate increased in response to the perturbation, then the

increase in heart rate resulted from the actions of a hormone. He would then compare the results in an animal with intact adrenal glands to those in an animal from which he had removed or tied off the blood vessels of the adrenal glands. From the difference in the heart rate responses of the two animals, he could infer that the hormone responsible for the increase in heart rate came from the adrenal glands. The amount of increase in the heart rate provided a measure of the amount of hormone released.

Because cutting the sympathetic nerves to the heart was an integral part of the experimental setup, Cannon could not appreciate the contribution of those nerves to regulation of the heart's functions. The experimental design also prevented him from recognizing that disabling one component of the sympathoadrenal system would activate the other compensatorily.

The notion spread afterward that the sympathoadrenal system is active only in emergencies. In fact, the sympathetic noradrenergic system, by way of release of its neurotransmitter, norepinephrine, works in a kind of dynamic balance with the parasympathetic nervous system and its neurotransmitter, acetylcholine, to modulate the rate of the heartbeat, even in people at rest. Levels of adrenaline in the bloodstream have not been found to correlate with resting heart rate.

Why Cannon Never Won a Nobel Prize

In 1930, the Mexican physician and physiologist Arturo Rosenblueth joined Cannon's lab at Harvard. Their efforts to

explain the dual actions of adrenaline as excitatory at some sites and inhibitory at others led to their proposal that adrenaline is released from sympathetic nerves but is modified in the affected target cells.

The chemical messenger would react with a hypothetical substance, H, to form “sympathin.” Cannon and Rosenblueth proposed that there are two types of H, HE and HI, which result in the formation of an excitatory substance, sympathin E, or an inhibitory substance, sympathin I.

They were wrong. The identification by von Euler of norepinephrine as the sympathetic neurotransmitter in 1946, for which he received a Nobel Prize in 1970, refuted the view that adrenaline is the sympathetic neurotransmitter. Cannon’s incorrect notion about sympathins did not disappear from the literature until the 1950s.

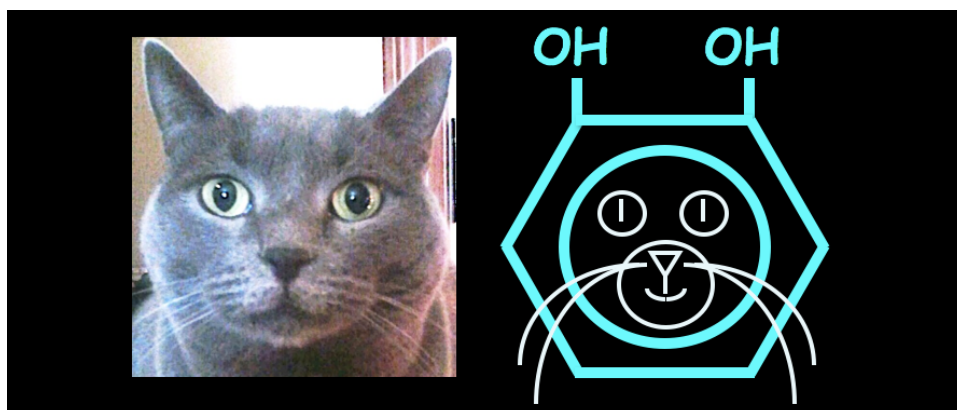
Because of the widespread acceptance of the notion of sympathins, when Raymond Ahlquist, based on his findings of two different orders of potency of seven sympathomimetic drugs in different tissues, postulated that there were two different receptors, alpha and beta, his paper, which challenged the validity of the concept of two kinds of sympathin, was initially rejected as being speculative.

How do Catechols Look Like Cats?

Members of the adrenaline family are catecholamines, and catecholamines are catechols.

The chemical, catechol, has a particular structure, consisting of a hexagon of carbon atoms with hydroxyl (OH) groups attached to adjacent points of the hexagon. The hexagonal ring is the face. The two hydroxyl groups are the pointy ears.

One way to remember what catechols look like is to picture their structure as the head of a cat.



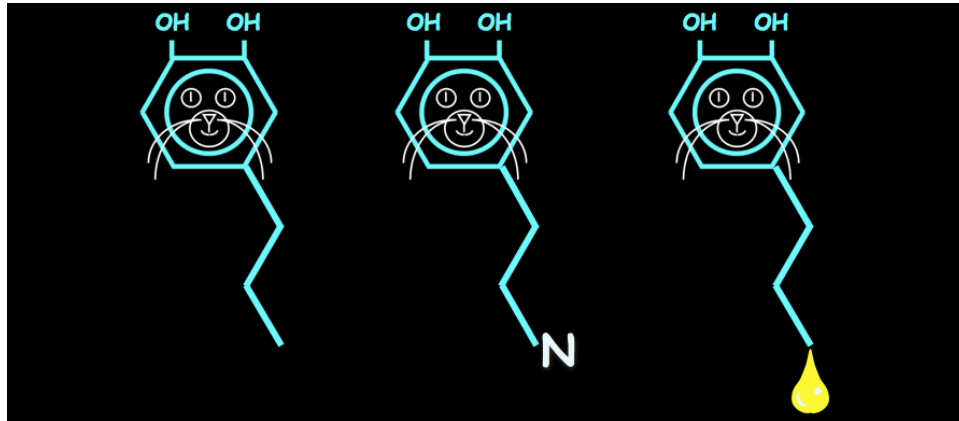
The chemical structure of catechol looks like a cat's head.

Catechol itself does not exist in the human body, but chemicals that contain catechol as part of their molecular structure are called catechols.

Catecholamines look like the entire cat, including its tail.

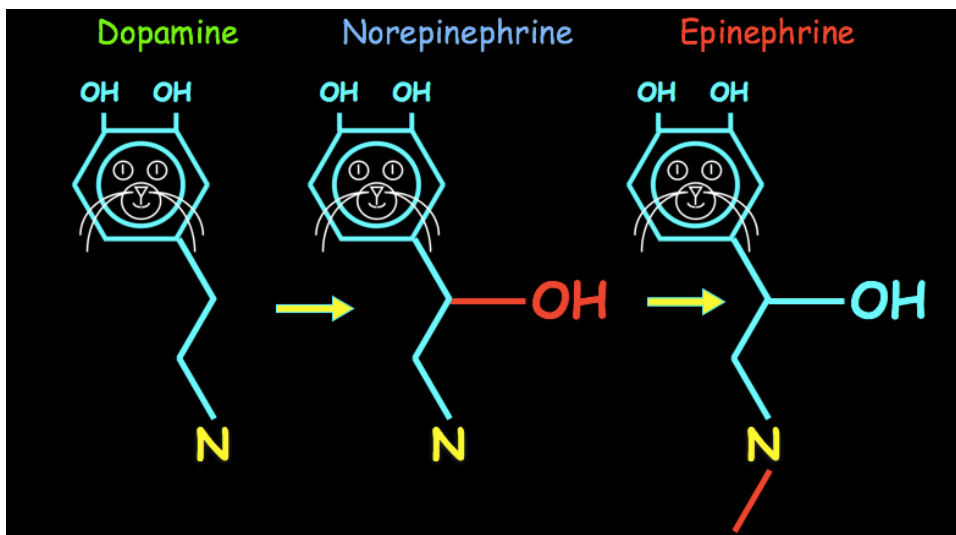
The tail of the cat is a short hydrocarbon strand, consisting of carbon and hydrogen atoms. At the end of the tail is an amine (ammonia) group. Think of a cat in its litter box, with the

ammonia coming off the tail end producing a smell like urine.



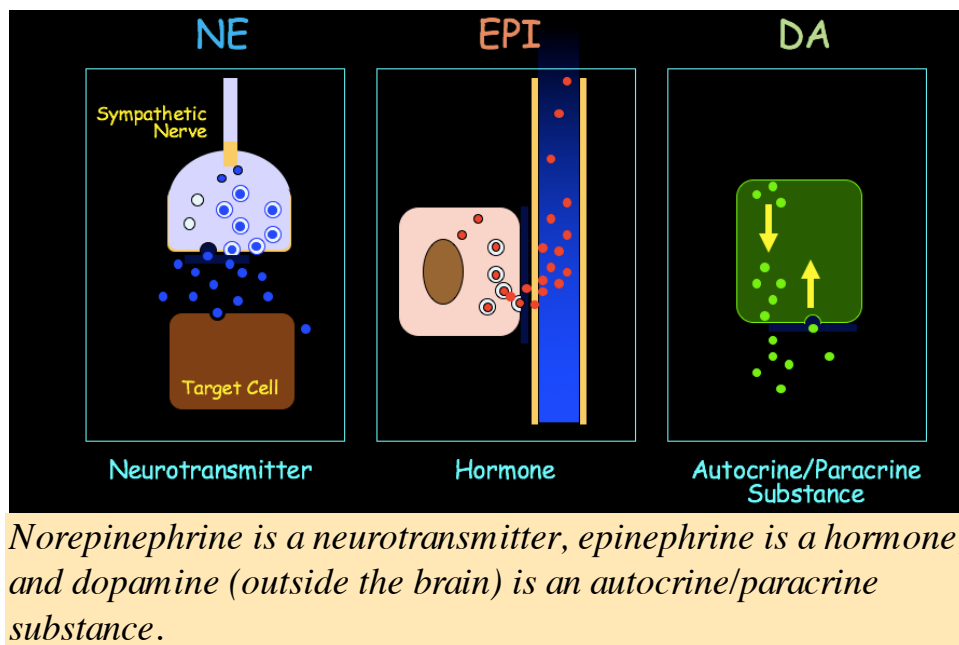
Catecholamines look like the entire cat, from head to tail. The catecholamine shown in the middle is dopamine.

The body's three catecholamines, dopamine, norepinephrine, and adrenaline, are like the grandfather, father, and son in a small chemical family. Adrenaline is derived from norepinephrine, and norepinephrine is derived from dopamine.



The catechols dopamine, norepinephrine, and epinephrine (adrenaline) are catecholamines.

The three catecholamines happen to represent three different ways the body regulates the inner world of the body. Norepinephrine is a neurotransmitter, released from nerves of the sympathetic nervous system and acting mainly locally on nearby target cells. Although a small proportion of the norepinephrine released from sympathetic nerves enters the bloodstream, norepinephrine in the bloodstream must reach relatively high concentrations before it exerts effects as a hormone.



Adrenaline is a hormone, released from the adrenal gland into the bloodstream and then swept by the bloodstream to organs and tissues throughout the body, where adrenaline produces a large variety of effects.

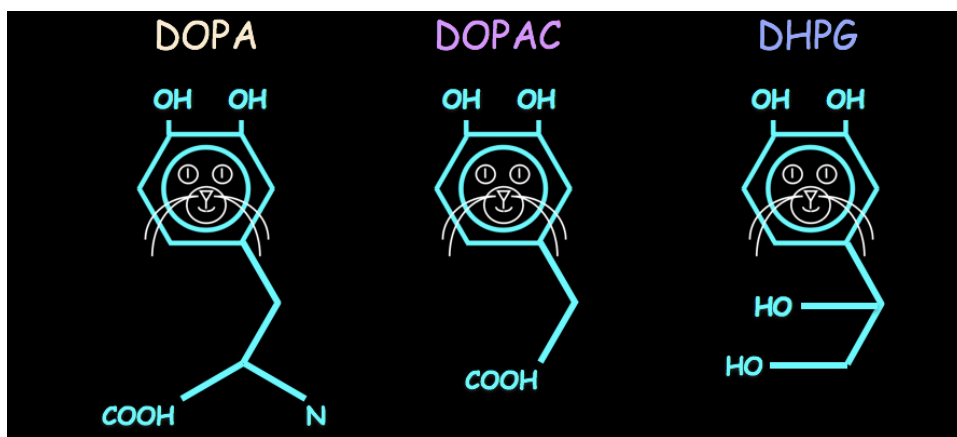
Outside the brain, dopamine appears to be an “autocrine/paracrine” substance, produced in, released from,

and acting locally on the same or nearby cells. Concentrations of dopamine in these organs have little to do with local nerves. In evolutionary terms, dopamine systems seem to date from before the time of nerve networks or hormones.

In nerves of the sympathetic noradrenergic system (SNS) dopamine is converted to norepinephrine, the main chemical messenger of the SNS.

Another catechol found in human plasma, urine, and cerebrospinal fluid is L-DOPA, the same chemical that as a drug (levodopa) is used to treat Parkinson's disease.

Two other catechols are breakdown products—metabolites—of the catecholamines. 3,4-Dihydroxyphenylglycol (DHPG) is a metabolite of norepinephrine and adrenaline, and 3,4-dihydroxyphenylacetic acid (DOPAC) is the main metabolite of dopamine in dopaminergic nerves.



Other catechols normally found in the plasma, urine, and spinal fluid are DOPA, DOPAC, and DHPG.

Within the brain, dopamine is an important neurotransmitter.

The discovery that dopamine is a neurotransmitter in the brain led to a Nobel Prize in 1970 for Arvid Carlsson.

Norepinephrine is also a neurotransmitter in the brain. .

Human plasma, urine, and cerebrospinal fluid all contain DOPA, DOPAC, and DHPG. DOPA, a catechol amino acid, is the precursor of dopamine. DOPAC, a catechol acid, is the main metabolite of dopamine in dopaminergic nerves. DHPG, a catechol alcohol, is the main metabolite of norepinephrine in noradrenergic nerves. Levels of each of these catechols have particular meanings in terms of the functions of catecholamine systems in the brain, heart, kidneys, and body as a whole.

Neuronal Soda Pop

This section describes the stations on the catecholamine assembly line—the steps in catecholamine biosynthesis.

To people with Parkinson's disease, DOPA (also called L-DOPA and levodopa) is a miracle drug. Within minutes, DOPA converts a shuffling, tremorous, slow-moving person with stooped posture to a vigorous, normally moving person with the head held erect.

I will never forget the first time I witnessed this phenomenon, while I was a medical student. Onstage at the beginning of the lecture, the professor introduced a patient with Parkinson's disease who had not yet taken levodopa that day. Slowly, unsteadily, and with assistance the patient then made his way up the steps of the amphitheater and exited the doors at the top. He took a dose of levodopa outside.

At the end of the lecture, the professor reintroduced the patient and asked him to walk down to the stage. The patient literally bounded down the steps; when he reached the stage he turned around swiftly to face the assembled students, like a pirouetting ballet dancer, with a broad grin on his face and his head held high. The audience erupted in applause.

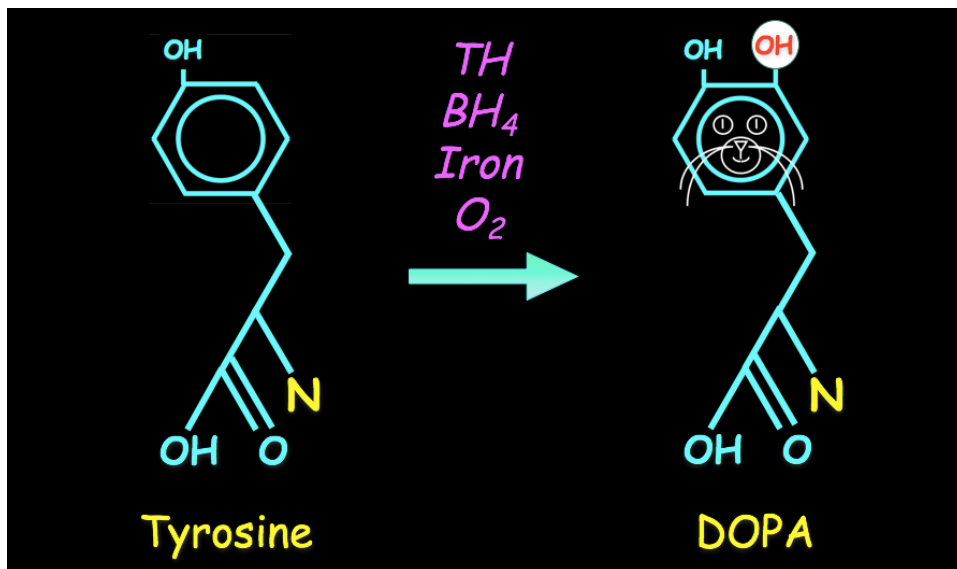
The body's catecholamines come from DOPA.

If you are a healthy adult human, then you are making your own levodopa all the time. The levels attained in the bloodstream, however, are about one-thousandth those required to treat Parkinson's disease.

All three of the body's catecholamines come from DOPA, and the DOPA comes from tyrosine, an amino acid. Amino acids are the building blocks of proteins. Tyrosine is an amino acid that is not a catechol. Tyrosine is converted to DOPA by the actions of an enzyme (a protein that speeds up a particular chemical process). The enzyme that speeds up the conversion of tyrosine to DOPA is tyrosine hydroxylase.

For tyrosine hydroxylase to work requires oxygen, iron, and tetrahydrobiopterin, abbreviated BH₄. BH₄ is a very important co-factor.

Deficiency of enzymes required to produce BH₄ can produce a pediatric neurodegenerative disease or else a particular movement disorder (called DOPA-responsive dystonia).

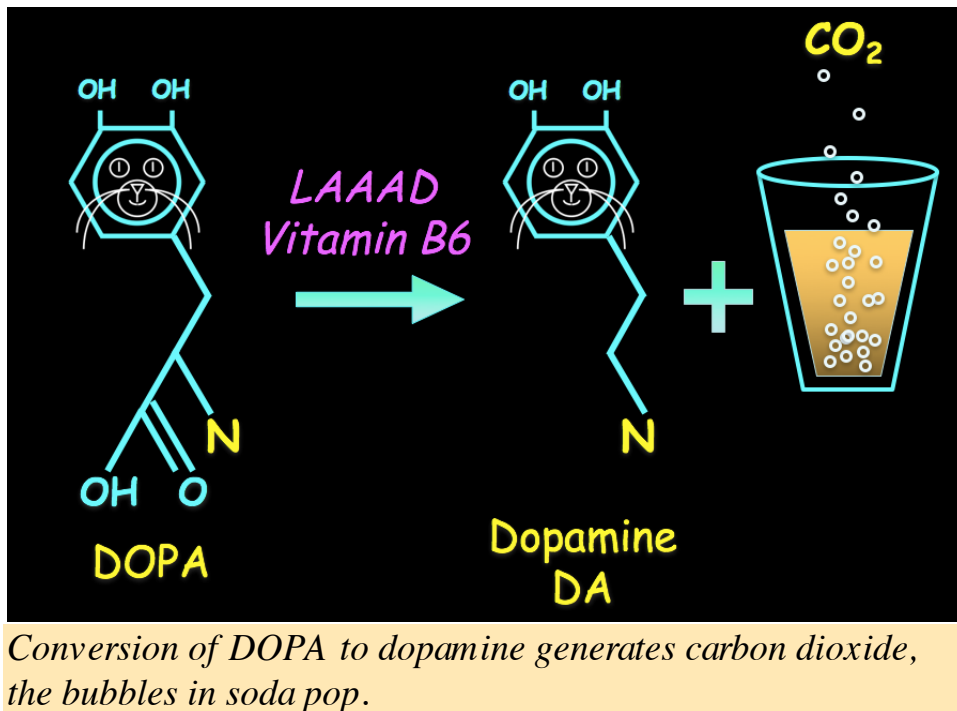


The first step in catecholamine synthesis is conversion of tyrosine to the catechol amino acid, DOPA.

CAT-A-COLA-MEANS

The next station on the catecholamine assembly line is the conversion of DOPA (which is a catechol but not a catecholamine), to dopamine, the grandfather in the catecholamine family. This step takes place in many types of cells and not just cells with the rest of the machinery required to store and recycle catecholamines.

To make dopamine from DOPA requires the enzyme, L-aromatic amino-acid decarboxylase (LAAAD, sometimes called DOPA decarboxylase, or DDC), and the co-factor pyridoxal phosphate, which is vitamin B6. (Incidentally, the word “vitamin” comes from “vital amine,” even though some vitamins, such as vitamin B6, are not amines at all.)



DOPA is a neutral amino acid, and it is taken up by all types of cells in the body, because all cells express the neutral amino acid transporter. Many cell types, such as kidney and liver cells, contain LAAAD, and so in several organs dopamine is made from the DOPA after uptake of the DOPA from the bloodstream.

The conversion of DOPA to dopamine involves cleaving off carbon dioxide from the molecule of DOPA. If this chemical reaction were carried out in a glass of water, the generated carbon dioxide gas would bubble up to the surface, like the effervescence in seltzer. Maybe this will help you remember that by this reaction, DOPA turns into a cat-a-COLA-mean.

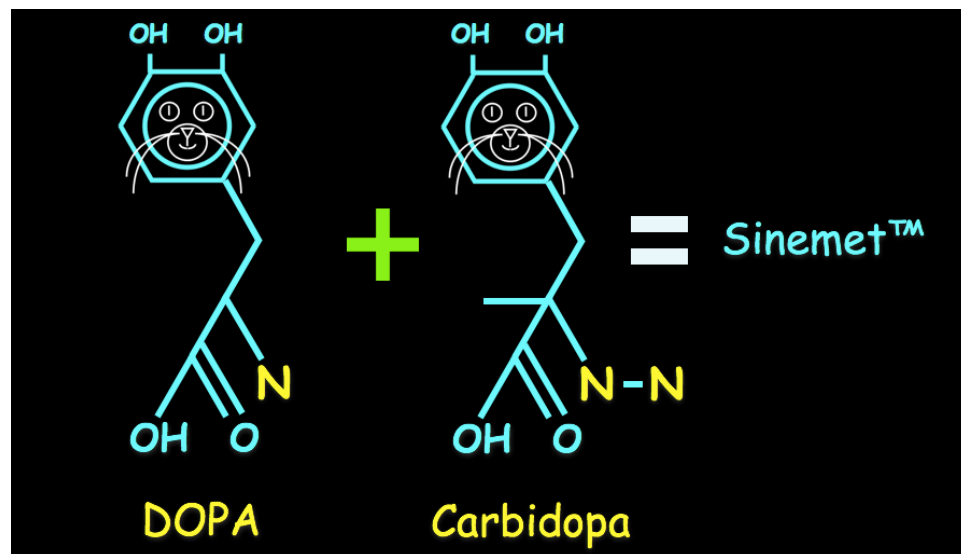
(Actually, because of the rapid oxidation of dopamine in solution to form a tan breakdown product, it might be better

think about the reaction generating ginger ale, but then there wouldn't be any pun with cola soda.)

WITHOUT VOMITING

A drug called carbidopa blocks LAAAD. Carbidopa is also a catechol.

Carbidopa does not cross the blood-brain barrier. This means that if a patient were to take DOPA with carbidopa, the DOPA would not be converted as efficiently to dopamine by LAAAD outside the brain, whereas DOPA that entered the brain could be turned into dopamine by LAAAD in brain cells.



DOPA combined with carbidopa is Sinemet™, from the words for “without vomiting.”

The combination of DOPA with carbidopa improves the efficiency of levodopa treatment for Parkinson's disease, while decreasing the toxic effects from too much dopamine being

made outside the brain.

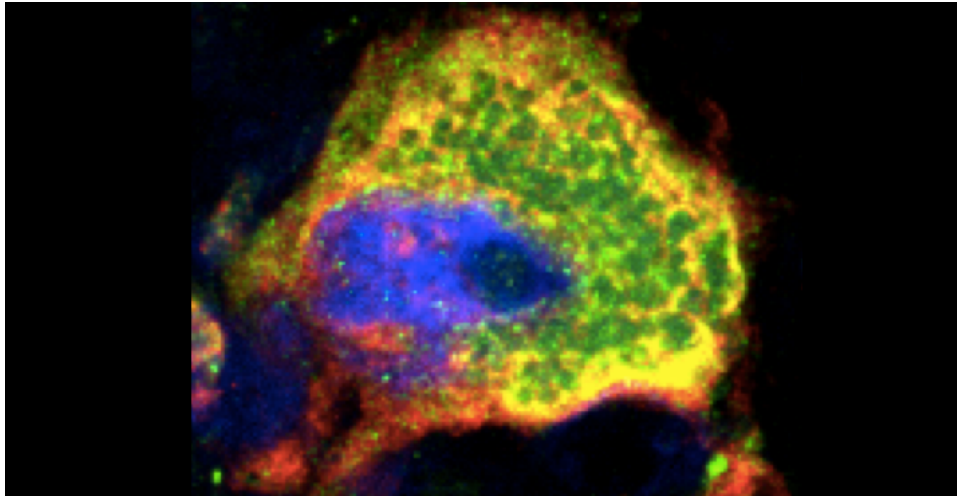
The main toxic effect of DOPA given as a drug is vomiting, because of production of dopamine from DOPA in the vomiting center, which lies outside the blood-brain barrier in the back of the brainstem. Giving carbidopa with DOPA decreases the amount of dopamine production from DOPA outside the brain and therefore helps prevent DOPA-induced vomiting. This explains one clever brand name for the levodopa-carbidopa combination to treat Parkinson's disease, Sinemet™. Sinemet is a combination of the Latin words for “without vomiting.”

Theoretically, carbidopa could prevent the production of all the catecholamines; however, at the doses used clinically it inhibits but does not block catecholamine production. In fact, because of the tremendously high plasma DOPA levels attained by oral levodopa, in patients taking Sinemet™ plasma levels of dopamine and its metabolites are actually substantially increased, not decreased.

THE WEAKEST LINK

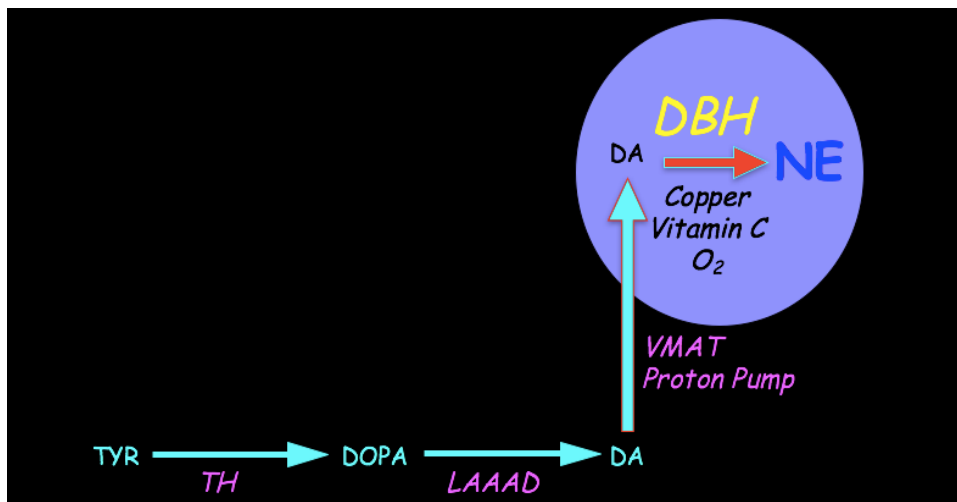
The next step in the production of norepinephrine and adrenaline is the most complex, because it requires not only a specific enzyme and co-factors but also physical movement of dopamine from the cytoplasm into the vesicles.

Norepinephrine normally is made within vesicles. This is because dopamine-beta-hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine, is localized to the vesicles in noradrenergic neurons and in cells of the adrenal



In this normal human sympathetic ganglionic neuron, blue is the nucleus, green is DBH, red TH, and yellow co-localized DBH with TH. The green spots correspond to DBH in vesicles. There is both DBH and TH in the cytoplasm (image courtesy of R. Isonaka).

medulla. In order to synthesize norepinephrine in the body, dopamine, which is made from DOPA in the cytoplasm, must be taken up into the vesicles.



Norepinephrine is made from dopamine within vesicles.

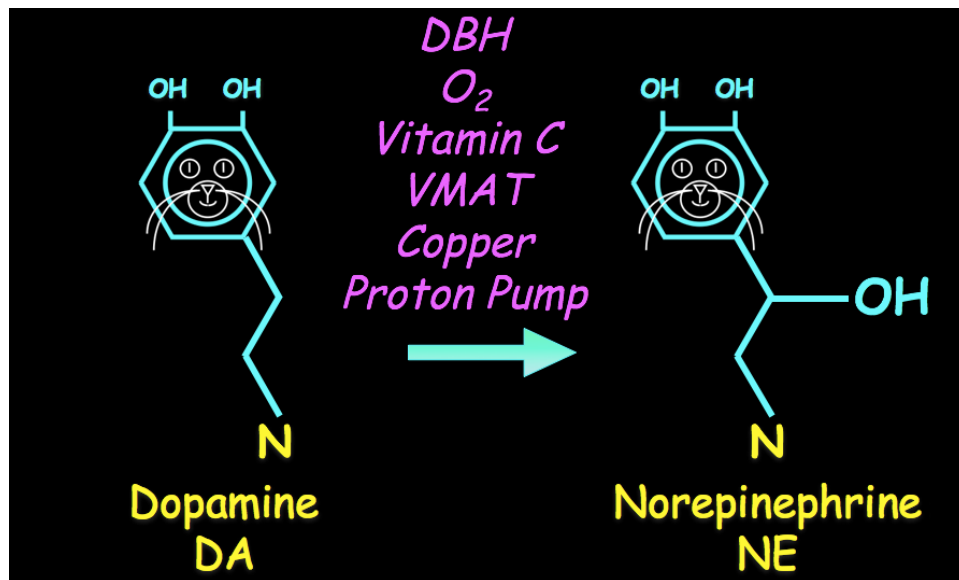
In sympathetic noradrenergic nerves and in the brain, uptake into the vesicles is mediated by a transporter called the type 2 vesicular monoamine transporters (VMAT2). The uptake is an energy requiring process, meaning that it requires adenosine triphosphate (ATP). The energy is used to pump protons into the vesicles by a proton pump. This makes the inside of the vesicles acidic. As the protons leak out of the vesicle, dopamine comes in via the VMAT. In contrast to norepinephrine, dopamine (and acetylcholine in cholinergic neurons) is produced in the cytoplasm.

DBH is a copper enzyme. In order to convert dopamine to norepinephrine, copper must be incorporated in the DBH molecule. In a pediatric diseases called Menkes disease there is a mutation of the gene encoding a form of copper ATPase, and this impairs incorporation of copper in DBH. Patients with Menkes disease do not synthesize norepinephrine normally, because copper doesn't meet up with DBH.

A variety of proton pump inhibitors (PPIs) are available by prescription or over the counter. Theoretically, they could interfere with vesicular uptake and thereby with norepinephrine synthesis.

I once had a patient in whom this may have been the case. He had physiological, neurochemical, and neuroimaging abnormalities consistent with decreased vesicular uptake and decreased norepinephrine synthesis, and I diagnosed him with probable pure autonomic failure. He was on a prescription PPI for severe gastroesophageal reflux.

I saw the patient in follow-up a couple of years later.



Several factors and processes are required in order to make norepinephrine from dopamine.

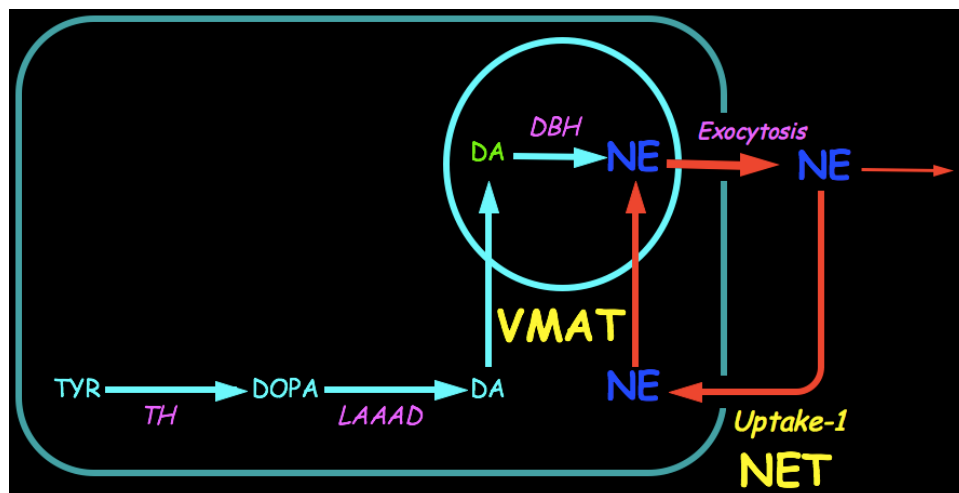
Sympathetic noradrenergic functions were now normal. In the interim he had undergone successful surgery for his gastroesophageal reflux, and so he no longer was on a PPI. I don't know of any studies that have looked formally into whether and if so which PPIs inhibit norepinephrine synthesis sufficiently to produce symptoms and signs of sympathetic noradrenergic failure.

Ascorbic acid (vitamin C) is a co-factor for DBH, and so it is theoretically possible that patients with scurvy have decreased norepinephrine synthesis. In normal volunteers deprived of vitamin C, however, there is no evidence of a problem with norepinephrine production.

A Better World Through Recycling

Several types of nerve cells recycle their chemical messengers. Sympathetic nerves possess an ingenious processing mechanism that simultaneously inactivates the released chemical messenger norepinephrine, recycles the norepinephrine, limits its actions spatially to a small volume, and modulates the amount of delivery of the neurotransmitter to the target cells for a given rate of release.

This processing mechanism is reuptake of the neurotransmitter from the fluid outside the cells (extracellular fluid). For discovering the role of neuronal reuptake, rather than simple metabolic breakdown by an enzyme, in the inactivation of neurotransmitters, Julius Axelrod received a Nobel Prize in 1970.



Norepinephrine recycling depends on the cell membrane norepinephrine transporter (NET) and the vesicular monoamine transporter (VMAT).

Axelrod carried out his Nobel Prize-winning work in the same venerable Building 10 where I sit.

The neuronal reuptake process is relatively specific for the particular neurotransmitter. One might even define the type of nerve cell by the neurotransmitter it takes up. For the catecholamines, norepinephrine, adrenaline, and dopamine, reuptake takes place by a process originally called “uptake-1” (in contrast with “uptake-2” by cells other than nerve cells).

Now we know that uptake-1 involves at least two different transporters, which physically transport the neurotransmitter molecules into the cells. The transporter for norepinephrine is called the cell membrane norepinephrine transporter, or NET. The transporter for dopamine is called the dopamine transporter, or DAT.

One of the peculiarities of the functioning of these transporters is that dopamine is more avidly taken up by the NET than norepinephrine is. We exploited this neurochemical quirk in developing a form of dopamine tagged with radioactivity, to visualize sympathetic nerves in people by PET scanning, as you will read about later. The sympathetic nerves take up the radioactive dopamine via the NET.

The catecholamine recycling process is completed by translocation of from the cytoplasm into storage vesicles by the VMAT. Because of the NET, the concentration of norepinephrine in the cytoplasm normally exceeds that in the fluid around noradrenergic cells by many-fold, and because of the VMAT, the concentration of norepinephrine in the vesicles

normally exceeds that in the cytoplasm also by many-fold. As a result of these processes acting in series, the concentration of norepinephrine in the storage vesicles normally is several thousand times the concentration in the extracellular fluid. Now that's recycling!

At least five types of perturbation interfere with catecholamine recycling, and each one exerts powerful effects both inside and outside the brain.

Several types drugs interfere with catecholamine recycling.



Len Bias, a star basketball player at the University of Maryland, died of acute cocaine cardiotoxicity.

The first is cocaine. Cocaine is a classic inhibitor of uptake-1. The heart depends heavily on uptake-1 to inactivate norepinephrine released from local sympathetic nerves, and cocaine administration can evoke severe heart problems, such as heart failure and even sudden cardiac death in apparently

healthy people.

A highly publicized example was Len Bias, the University of Maryland basketball star who died of the cardiac toxic effects of cocaine.

The second is a class of drugs used clinically for depression called tricyclic antidepressants. Some tricyclics are desipramine, imipramine, nortriptyline, and amitriptyline (brand names Norpramin, Tofranil, Pamelor, and Mylan).

Another antidepressant that is not a tricyclic but is thought to work at least partly by inhibiting the NET is venlafaxine (Effexor). In general, tricyclic antidepressants inhibit uptake-1 but also decrease sympathetic nervous system outflows from the brain. As a result, they do not produce nearly as great an increase in the delivery of norepinephrine to its receptors in the heart as cocaine does.

The third is a type of drug that blocks the VMAT. Reserpine is the classic example of this type of drug. By depleting the stored chemical messengers outside the brain, reserpine usually drops blood pressure, and by depleting messengers inside the brain, it can produce inactivity and depressed mood (as illustrated in “the case of the depressed dog” discussed later in this section).

Tetrabenazine (Xenazine™), an FDA approved drug for Huntington’s disease-related chorea that has been used for other hyperkinetic movement disorders, inhibits the type 2 VMAT, VMAT2. Theoretically, tetrabenazine should decrease

norepinephrine synthesis, but whether at clinically used doses tetrabenazine affects plasma or cerebrospinal fluid levels of norepinephrine or its metabolites does not appear to have been studied.

The fourth is a genetic mutation of the NET. This has been described so far in one and only one family. Because of decreased ability to recycle norepinephrine, people with this mutation have excessive delivery of norepinephrine to its receptors in the heart in situations that activate sympathetic nervous system outflows.

One of these situations is simply standing up, and so NET deficiency constitutes a rare cause of postural tachycardia syndrome (POTS), in which an inability to tolerate prolonged standing (orthostatic intolerance) is coupled with an excessive heart rate response to standing (postural tachycardia).

Among other findings in POTS with NET deficiency is a tendency to panic, possibly associated with excessive delivery of catecholamines to their receptors.

The fifth is excessive “leakiness” of the storage vesicles. Normally, because of the enormous concentration of norepinephrine in storage vesicles, norepinephrine leaks passively out of the vesicles at a high rate into the cytoplasm. Correspondingly, however, by way of the efficient VMAT, the norepinephrine is taken back up into the vesicles. For the VMAT to function requires a concentration gradient for hydrogen ion between the cytoplasm and the inside of the vesicles, with the vesicle contents acidic. In any situation in

which the cytoplasm becomes acidic, such as anoxia (lack of oxygen), exposure to some poisonous agents, or (perhaps) proton pump inhibition, there is increased net leakage from the vesicles, which could deplete sympathetic noradrenergic nerves of their neurotransmitter. Theoretically, any problem with the mitochondria, the organelles within cells that produce chemical energy, could interfere with vesicular storage, because vesicular uptake requires energy, whereas leakage from the vesicles is passive.

THE CASE OF THE DEPRESSED DOG

About a quarter century ago I was exploring whether a particular chemical our group had developed, an analog of dopamine tagged with radioactivity (^{18}F -dopamine, which you'll read about much more later), could successfully visualize sympathetic nerves by a special type of nuclear medicine scan called a PET scan.

To test this idea, I did a ^{18}F -dopamine PET scan of a dog that had just been treated with a dose of the drug reserpine. Reserpine exerts a highly specific effect in the body. It prevents uptake of a class of neurotransmitters called monoamines (catecholamines and serotonin are the main monoamines in the body) into storage vesicles. If my hypothesis were correct, then treatment with reserpine would prevent uptake of the radioactive dopamine into the vesicles and therefore prevent visualization of the sympathetic nerves.

In conducting this experiment, I didn't appreciate adequately that reserpine also rapidly gets into the brain. When the testing

was over the dog was returned to its kennel. Soon afterward I received a phone call from a very concerned veterinarian. She reported that dog was lying listless in a corner. Its tail was tucked underneath it, and it wouldn't wag its tail when a caretaker approached. It was poorly responsive, it wouldn't eat, and its blood pressure was low. The veterinarian thought the dog was seriously ill.

Instead it seemed to have a form of acute depression. Reserpine rapidly depletes brain levels of the monoamines norepinephrine, dopamine, and serotonin. Depletion of dopamine causes decreased spontaneous movement, decreased oral intake, and a tendency to depression. Depletion of norepinephrine decreases vigilance behavior and also can cause a tendency to depression. Depletion of serotonin probably also depresses mood. Depletion of all three chemicals in the brain likely produced the depressed affect in the dog.

Because of reserpine-induced blockade of norepinephrine recycling in the dog's sympathetic noradrenergic system, the nerves became depleted of norepinephrine. This probably was the basis for the low blood pressure in the poor dog. Indeed, the leaf of the plant from which reserpine was isolated, *Rauwolfia serpentina*, was one of the first successful medicinal treatments for clinical hypertension.

Stress Vitamins

Production of adrenaline and other catecholamines in the body requires some vitamins and minerals. Endogenous dopamine comes from DOPA, and to make DOPA requires the mineral

iron. Production of dopamine from DOPA, and therefore production of all the catecholamines, depends on the availability of pyridoxal phosphate, which is vitamin B6. The conversion of dopamine to norepinephrine in the body requires ascorbic acid (vitamin C) as well as the minerals magnesium and copper.



“Stress” formulas contain vitamins B6 and C.

As near as I can tell, all “stress formulas” contain vitamins B6 and C.

Of Mice and Men and Wine and Cheese

Although catecholamines are recycled efficiently in sympathetic nerves, a small percent of norepinephrine and dopamine in the cytoplasm of sympathetic nerves undergoes metabolic breakdown by a process that is sped up by the enzyme, monoamine oxidase (MAO). MAO is found in the

outer membrane of the mitochondria, the cell's energy plants.

In the brain, MAO plays a key role in mood, and drugs that inhibit MAO are effective anti-depressants.

Genetic deficiency of MAO-A causes severe hyperactivity and aggressiveness, in mice and men. A Dutch family with this deficiency attained notoriety for antisocial behavior, murder, and violent rape.

I use the phrase “mice and men” here, because the genes for MAO-A and MAO-B are on the X chromosome. Males have one X chromosome and one Y chromosome. In boys with a mutation of the gene encoding MAO-A on their single X chromosome, the disease is expressed. Girls have two X chromosomes. In girls, if the same mutation occurred on one of their two X chromosomes, the other chromosome would still encode MAO-A, and the disease would not be expressed (they would be asymptomatic carriers). This means that in the family with “bad seed” from mutation of the MAO-A gene, girls would not have the disorder, half of the at-risk boys would, and the disease would skip generations.

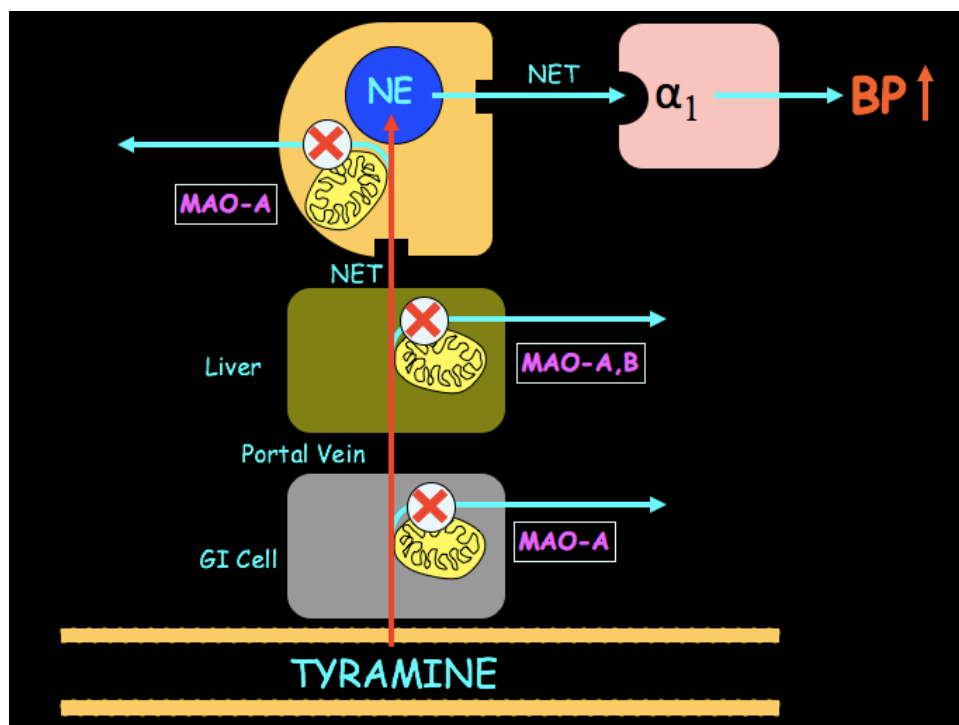
WHEN NOT TO ATTEND A WINE AND CHEESE PARTY

No discussion of MAO would be complete without wine and cheese.

Red wine and hard cheeses contain an abundance of a chemical called tyramine. Tyramine is an indirectly acting

sympathomimetic amine. That is, it doesn't exert effects by itself, but it increases release of norepinephrine from sympathetic nerves. The released norepinephrine increases the blood pressure and the force of the heartbeat.

Ordinarily, relatively little of ingested tyramine makes its way to the bloodstream because of an effective "gut-blood barrier,"



The "cheese effect." If MAO is inhibited, tyramine in cheese can displace norepinephrine in sympathetic nerves, increasing blood pressure.

which includes a variety of enzymes, one of which is MAO. Patients taking an MAO inhibitor have a relatively permissive gut-blood barrier for dietary substances that normally would be broken down by MAO in the gut or liver. In the setting of

MAO inhibition, dietary tyramine can penetrate the gut-blood barrier and reach sympathetic nerves. Once inside the nerves, tyramine in the cytoplasm gets taken up into the vesicles by way of the vesicular monoamine transporter (VMAT), and inside the vesicles tyramine accelerates leakage of norepinephrine from the vesicles, possibly by alkalinizing the vesicles and decreasing the hydrogen ion gradient required for concentrating norepinephrine in the vesicles. Norepinephrine then builds up in the cytoplasm and can go backward through the NET to reach the fluid surrounding the cells, or it can exit the cell from vesicles that are fused with the membrane surface and have the “omega sign” opening them to the extracellular fluid. By these mechanisms, norepinephrine is delivered to its receptors on cardiovascular cells, and the blood pressure and the force of the heartbeat increase.

In people taking an MAO inhibitor, such as for depression, ingestion of tyramine can produce a paroxysmal increase in blood pressure or evoke a dangerously abnormal heart rhythm. This is why if you were taking an MAO inhibitor for depression, you wouldn’t want to attend a wine and cheese party.

There are two genes for MAO, which are near each other on the X chromosome, and there are two corresponding forms of MAO, called MAO-A and MAO-B. Sympathetic nerves express only MAO-A, whereas many other cell types express both forms. It is thought that the enzymatic gut-blood barrier for tyramine depends mainly on MAO-A. Theoretically, the “cheese effect” would apply only to drugs that inhibit MAO-A or inhibit both forms of MAO. In particular, selegiline (also

called l-deprenyl, brand name Eldepryl) and rasagiline (brand name Azilect), which are used to treat Parkinson's disease, are relatively selective MAO-B inhibitors; they are much less likely to cause a cheese effect than are drugs that inhibit MAO-A.

Autotoxicity: A Test Drive

In dopamine neurons, MAO converts dopamine to the aldehyde, 3,4-dihydroxyphenylacetaldehyde (DOPAL).

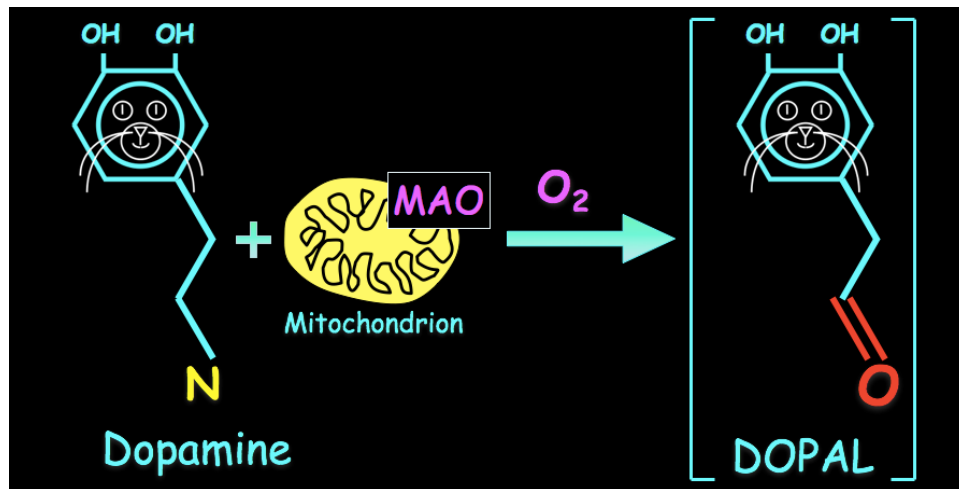
THE CATECHOLALDEHYDE HYPOTHESIS

DOPAL is toxic and is the focus of the “catecholaldehyde hypothesis,” a proposed explanation for the death of dopamine neurons in Parkinson's disease.

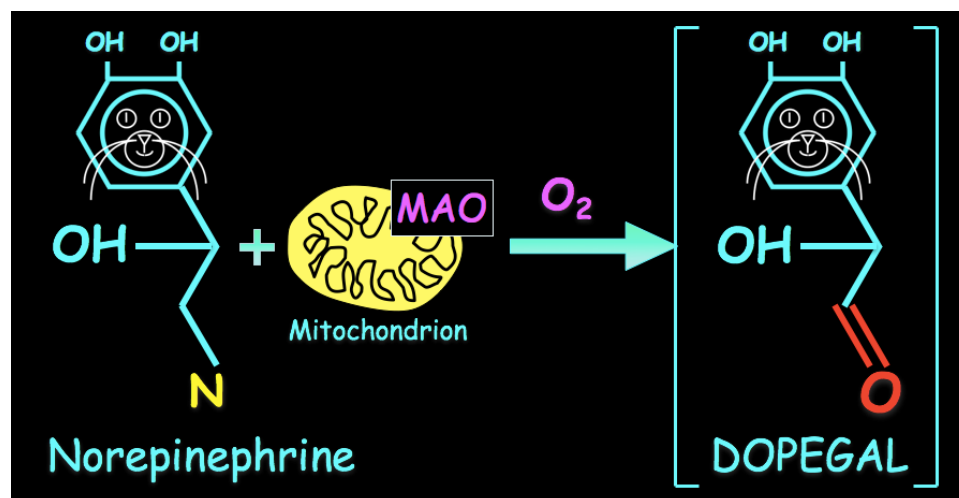
Later we will go over the catecholamine autotoxicity theory in some detail. The discussion here is just a test drive. (That was funny.)

In noradrenergic neurons, MAO converts norepinephrine in the cytoplasm to 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL). DOPEGAL is very unstable—so unstable that researchers haven't yet been able to examine whether it is an autotoxin, because it hasn't been available in pure form.

Just as dopamine and norepinephrine are metabolized by MAO to form potentially toxic aldehydes, serotonin (5-hydroxytryptamine, 5-HT) which is a monoamine that is not a catecholamine, is metabolized by MAO to form another aldehyde, 5-HIAL. Because of this, the catecholaldehyde



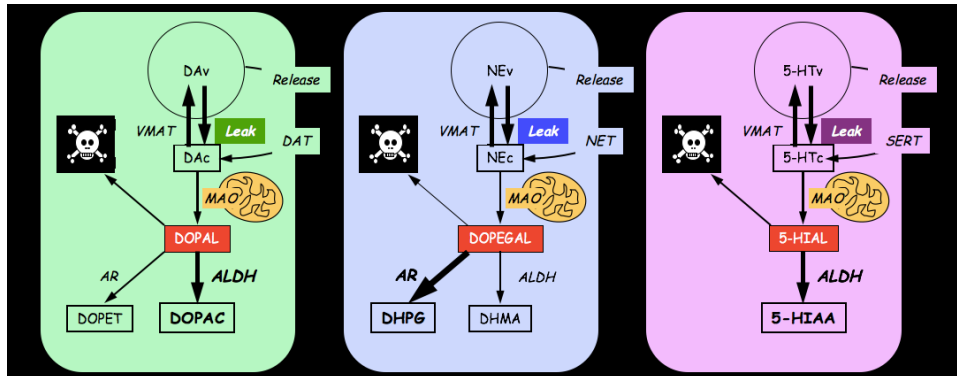
MAO acts on dopamine to form the intermediate metabolite, DOPAL. DOPAL is toxic.



MAO acts on norepinephrine to form the intermediate metabolite, DOPEGAL. DOPEGAL also is an aldehyde and probably also is toxic. It's too unstable to tell.

hypothesis can be expanded to the “monoamine aldehyde hypothesis.”

In Parkinson's disease, not only are dopamine neurons lost but so are norepinephrine and serotonin neurons. The monoamine aldehyde hypothesis explains this in terms of autotoxicity evoked by DOPAL, DOPEGAL, and 5-HIAL.



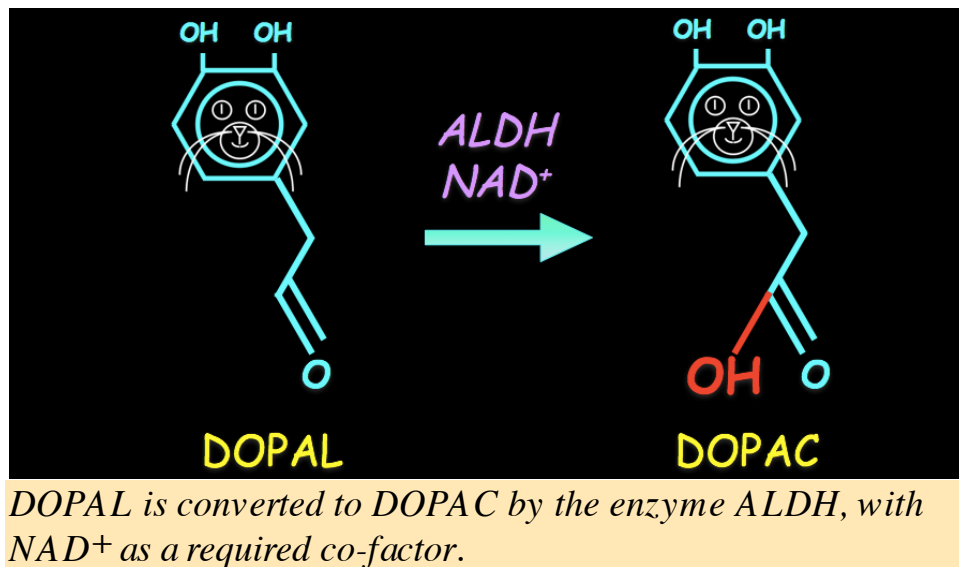
According to the monoamine aldehyde hypothesis, aldehydes produced by the action of MAO on dopamine, norepinephrine, and serotonin explain the vulnerability of monoaminergic neurons in Parkinson's disease.

DOPAL is rapidly and efficiently metabolized to the catechol acid, DOPAC. The enzyme responsible for this conversion is aldehyde dehydrogenase (ALDH).

Aldehydes like DOPAL are toxic, and yet they are made continuously in catecholamine neurons, because of the continuous appearance of the catecholamines in the cytoplasm. DOPAL is detoxified by ALDH. It is not surprising that in humans there are 19 different genes encoding forms of ALDH.

For ALDH to work requires a co-factor called NAD^+ . NAD^+ in turn is made in the mitochondria by an important process called complex 1. Drugs that inhibit complex 1 are toxic. Part of the toxicity in dopamine neurons may come from decreased

availability of NAD^+ for ALDH to do its job in preventing buildup of DOPAL.

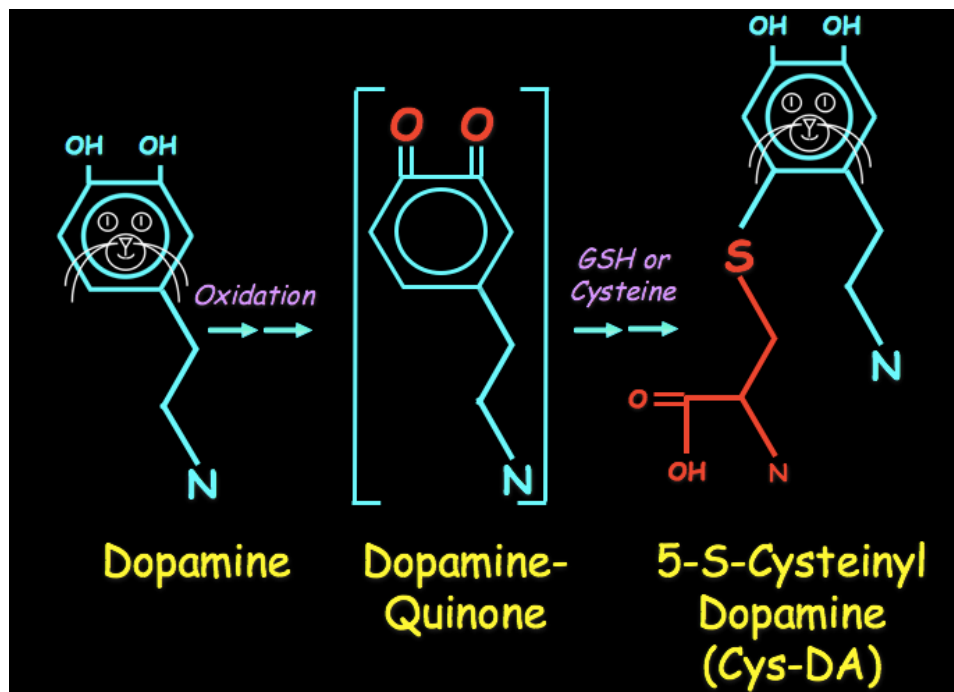


The product of ALDH acting on DOPAL is the catechol acid, DOPAC, and DOPAC is actively extruded from the cell. The enzyme series of MAO and ALDH acts lack a second detoxification system besides vesicular uptake, to keep cytoplasmic dopamine levels low.

SPONTANEOUS OXIDATION

Because of vesicular uptake and the enzymatic series of MAO followed by ALDH, levels of dopamine in the cytoplasm normally are kept extremely low.

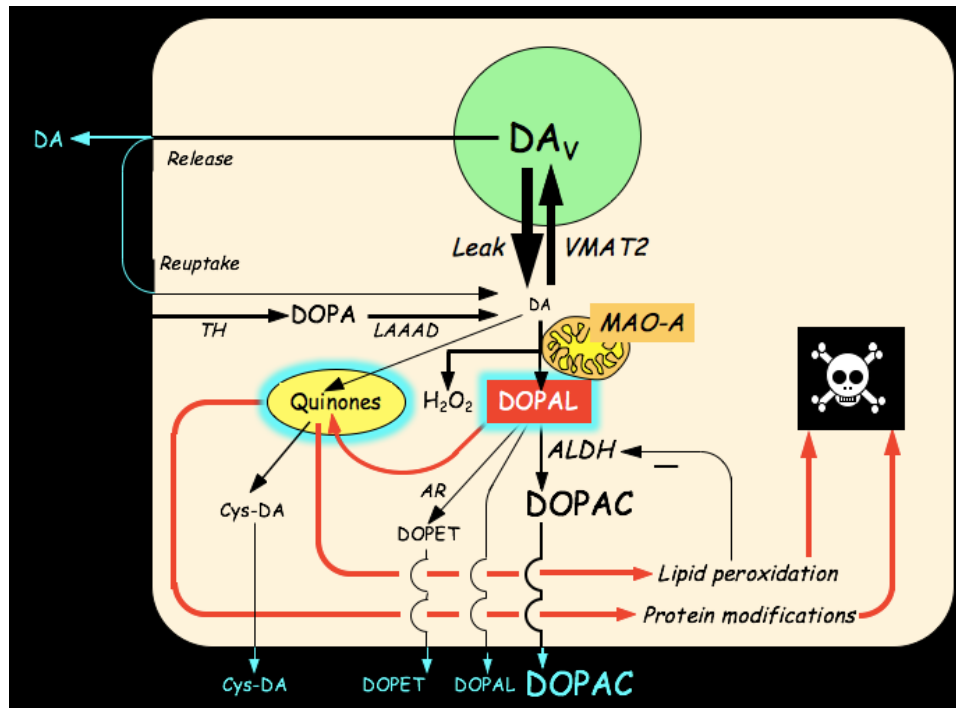
Dopamine and DOPAL in the cytoplasm can oxidize spontaneously to form quinones (dopamine-quinone, DA-Q, and DOPAL-quinone, or DOPAL-Q). The $-\text{OH}$ groups (the



Dopamine oxidizes spontaneously to form an unstable intermediate, dopamine-quinone (DA-Q). DA-Q reacts with glutathione (GSH) or cysteine to form 5-S-cysteinyl dopamine (Cys-DA).

pointy ears on the head of the cat) are replaced by =O groups.

Quinones are highly unstable and reactive compounds. DA-Q can bind with the amino acids glutathione or cysteine, eventually to form 5-S-cysteinyl-dopamine (Cys-DA). DA-Q can also be converted to chemicals called chromes and indoles and to polymers such as melanin and polydopamine. DOPAL-Q interacts with a variety of proteins, altering their functions.



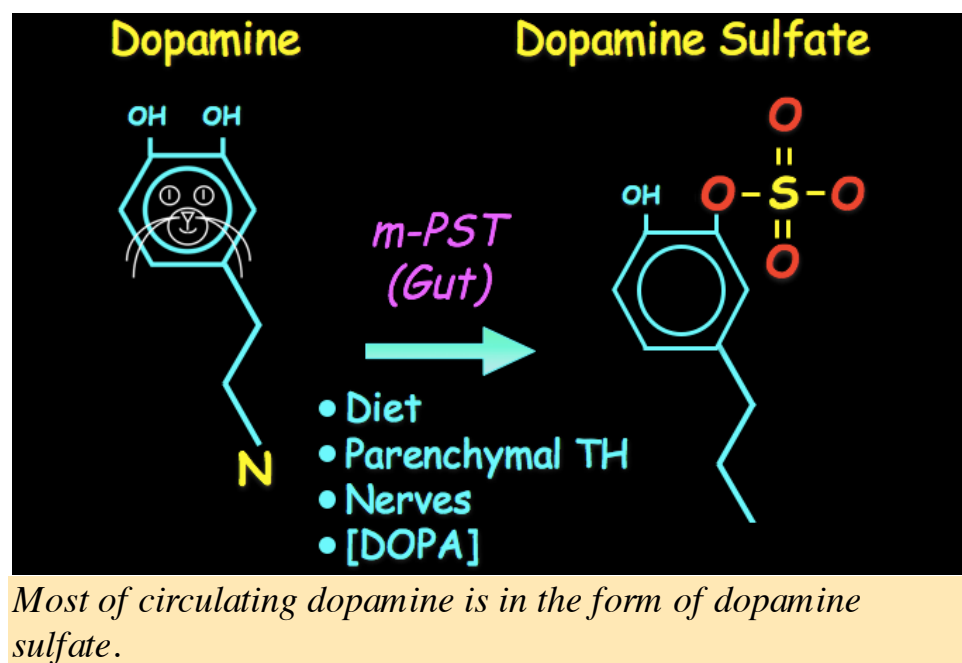
Overview of the catecholamine autotoxicity theory. According to this theory, products of enzymatic or spontaneous oxidation of dopamine are “suicide chemicals” that kill the neurons that contain them.

Three Surprises about Dopamine Metabolism

One of the surprising facts about dopamine metabolism in the body is that most of the synthesis and metabolism of dopamine takes place not in the brain or in the autonomic nervous system—in fact not in nerves at all—but in non-neuronal cells of the gut. The functions and regulation of this non-neuronal dopamine system are poorly understood.

Metoclopramide, an antagonist at dopamine receptors, is used

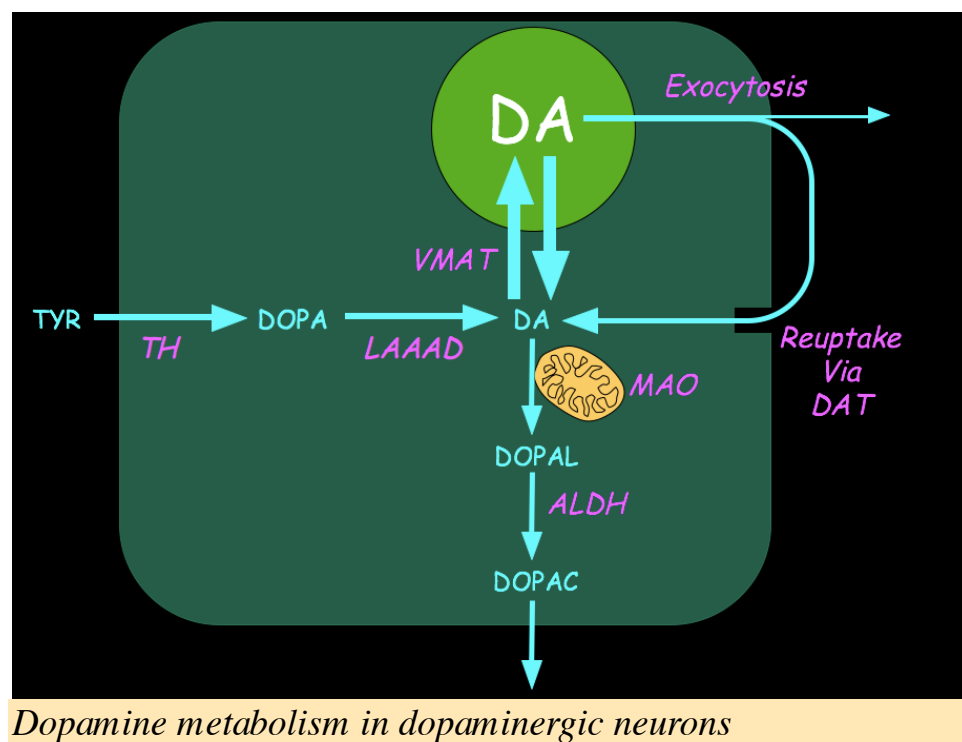
clinically to treat gastroesophageal reflux and delayed gastric emptying (gastroparesis). The drug increases lower esophageal sphincter tone, increases the amplitude of stomach contractions, and increases peristalsis in the small intestine, while relaxing the pyloric sphincter and duodenal bulb. From these effects, one may guess that endogenous dopamine produced in the gut may function to inhibit movement of food through the GI tract.



A second surprising fact about dopamine metabolism is that there is a very large amount of DOPAC in the urine—far more than can be accounted for by filtration of DOPAC in the plasma reaching the kidneys. Most of the dopamine, and probably most of the DOPAC, in the urine comes from uptake and decarboxylation of circulating DOPA by non-neuronal cells in the kidneys, in the renal DOPA-dopamine autocrine/paracrine system.

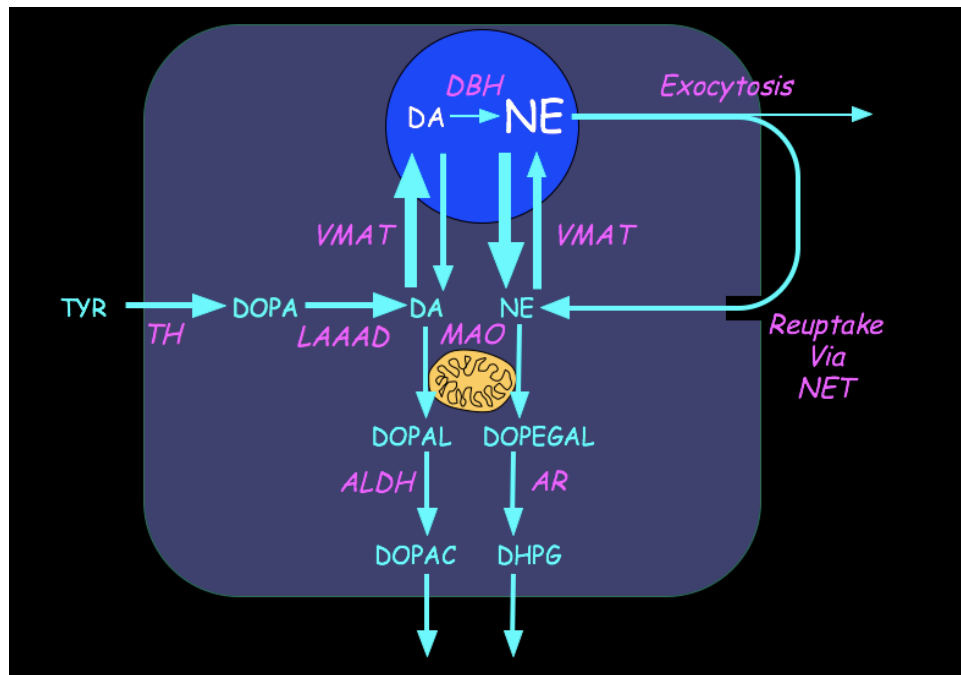
A third surprising fact about dopamine metabolism is that virtually all of the dopamine in the plasma exists not in free form but as a conjugated form—dopamine sulfate. The conjugation takes place in the gut via an enzyme called monoamine-preferring phenolsulfotransferase (mPST).

Metabolic Differences Between NE vs. DA



In many ways metabolism of norepinephrine resembles that of dopamine, but there are a few differences.

As a glycol, DHPG readily crosses cell membranes. In non-neuronal cells, which contain COMT, DHPG is methylated to form 3-methoxy-4-hydroxyphenylglycol (MHPG), with S-adenosyl methionine (SAME) serving as the methyl group

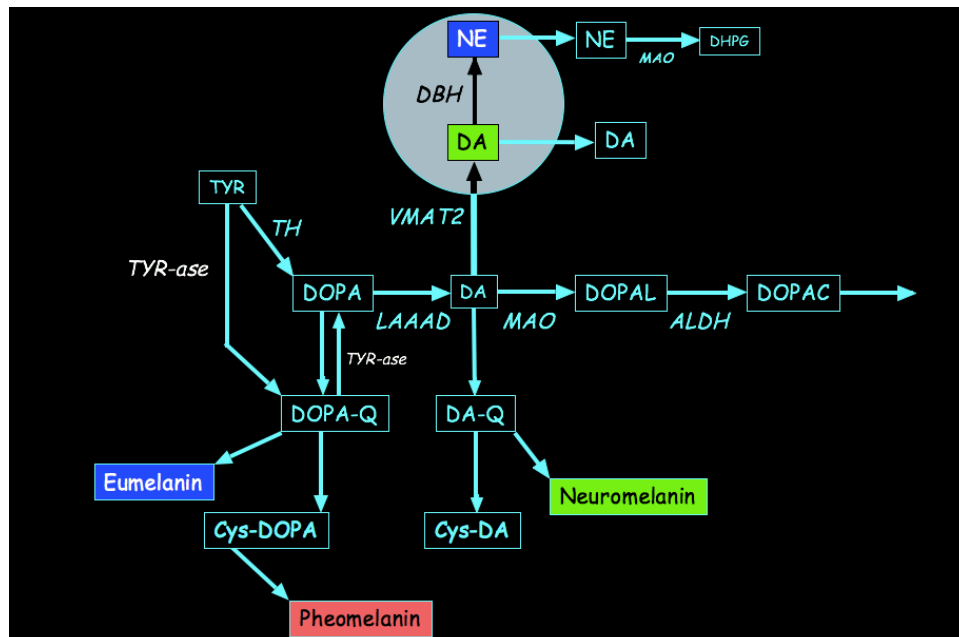


Norepinephrine metabolism in noradrenergic neurons

donor. In the liver, MHPG is converted to vanillylmandelic acid (VMA) by alcohol dehydrogenase and ALDH.

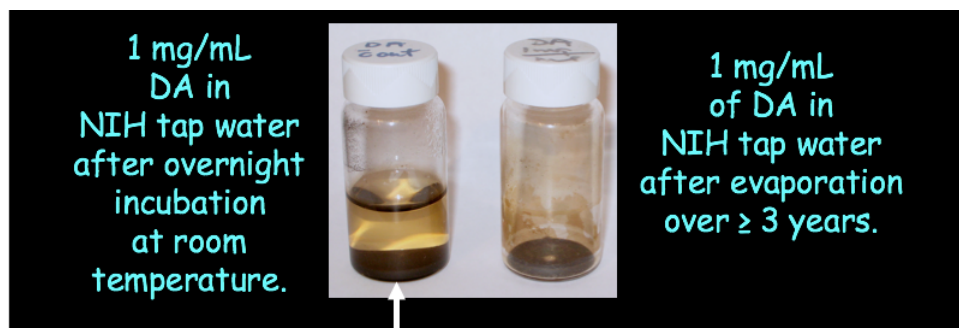
Melanins

Most of the metabolism of catecholamines in the body reflects cascades of enzymes acting in parallel and in series, such as MAO, ALDH, COMT, and m-PST. These enzymes, and vesicular sequestration mediated by the VMAT, keep cytoplasmic concentrations of catecholamines very low. A small proportion of catecholamine metabolism occurs by a non-enzymatic route—spontaneous oxidation.



Melanins are pigmented polymers that form in dopaminergic neurons.

When catechols such as DOPA and dopamine oxidize spontaneously, they form quinones. DOPA quinone and dopamine quinone are unstable and can polymerize to form large chemicals called melanins.



Dopamine spontaneously polymerizes to form a black pigment – a “substantia nigra.”

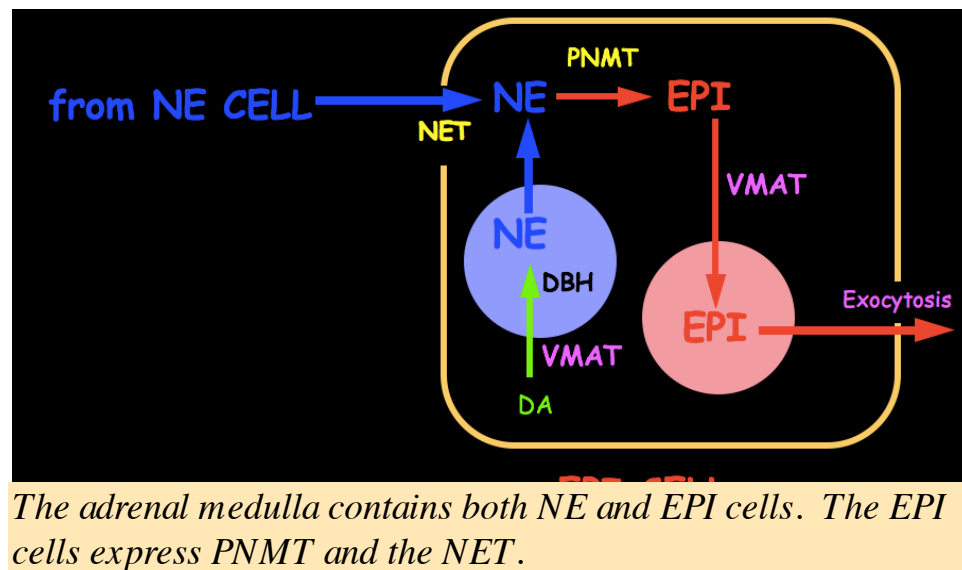
Melanin comes from the Greek word for “black.”

Neuromelanin is produced in the cytoplasm from the spontaneous oxidation of dopamine. Loss of black pigment in the substantia nigra (from the Latin for “black substance”) is a pathologic hallmark of Parkinson’s disease, probably because of the loss of dopaminergic neurons that contain neuromelanins.

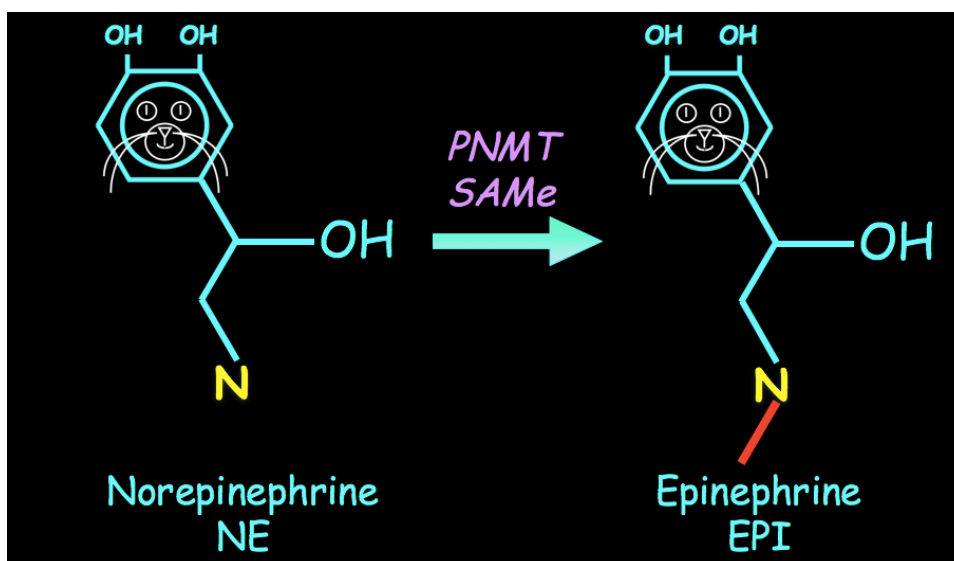
The Special Case of the Adrenal Medulla

The synthesis of adrenaline (epinephrine, EPI) by cells of the adrenal medulla is rather complicated, and the metabolism of catecholamines in adrenomedullary cells is different from the metabolism of catecholamines in sympathetic nerves or in catecholamine neurons in the central nervous system.

Epinephrine is made in the cytoplasm by the action of the enzyme phenylethanolamine-N-methyltransferase (PNMT) on norepinephrine.



S-adenosyl methionine (SAMe) is the methyl group donor. This doesn't mean that EPI is made from norepinephrine that has leaked from the vesicles into the cytoplasm. The adrenal medulla contains NE-producing and EPI-producing cell populations. Only the EPI-producing cells express the NET. This raises the possibility that EPI can be made in the cytoplasm from NE taken up into the cells via the NET.

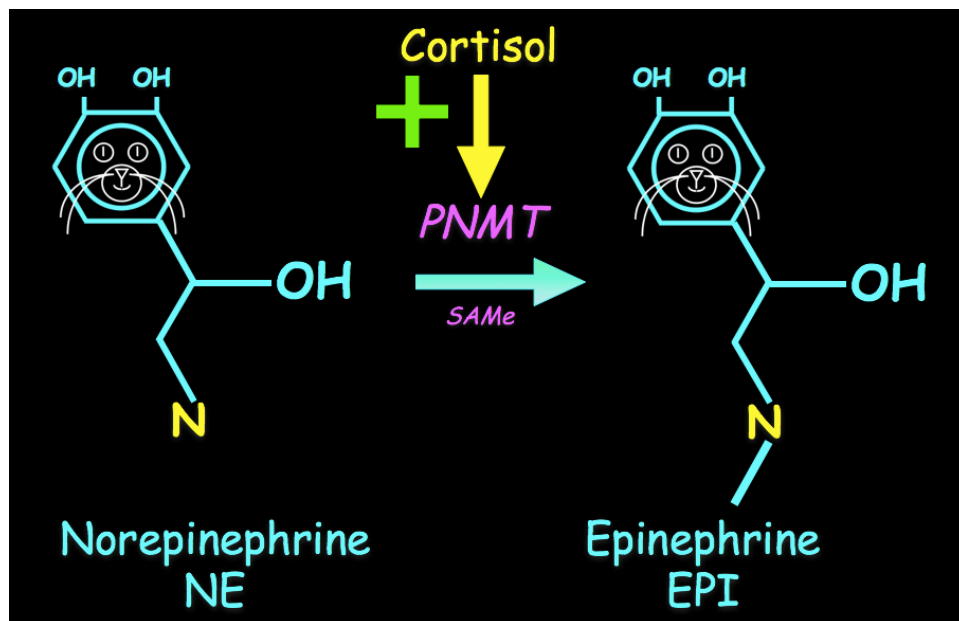


Norepinephrine is converted to epinephrine via phenylethanolamine-N-methyltransferase (PNMT), with SAMe as the methyl group donor.

Adrenomedullary cells express catechol-O-methyltransferase (COMT), whereas sympathetic nerves and catecholamine neurons in the central nervous system do not. As a result, adrenaline in the cytoplasm of adrenomedullary cells can be converted to metanephrine, and norepinephrine can be converted to normetanephrine.

Because of the ongoing leakage of catecholamines from the

vesicles into the cytoplasm, in the adrenomedullary cells metanephrine and normetanephrine are made all the time, even in the absence of catecholamine release. This explains why plasma levels of metanephrines (unconjugated normetanephrine and metanephrine) are sensitive indices of pheochromocytoma.



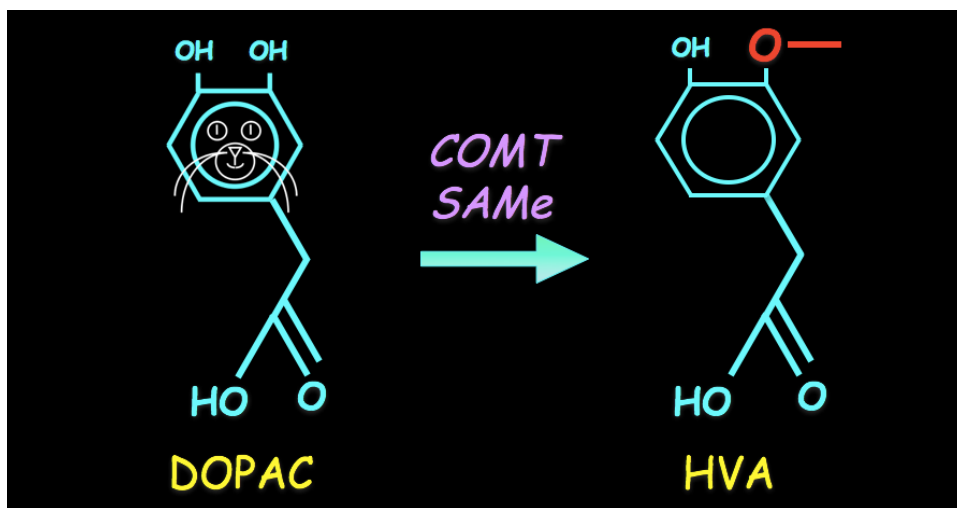
Cortisol is trophic for PNMT and promotes EPI synthesis.

Blood flow in the adrenal gland goes from the cortex through the medulla. As a result, adrenomedullary cells normally are bathed in high concentrations of adrenocortical steroids. Cortisol, the main glucocorticoid in the human adrenal cortex, is trophic for PNMT.

In addition, the adrenal medulla contains abundant receptors for angiotensin II, and angiotensin II evokes secretion of catecholamines. Adrenomedullary function therefore seem to be more susceptible than sympathoneural function to hormonal influences.

The Ends of the Lines

Non-neuronal cells contain an enzyme called catechol-O-methyltransferase, or COMT. COMT transfers a methyl group to DOPAC, with S-adenosyl-methionine (SAME) serving as the methyl group donor, to form homovanillic acid (HVA). HVA is the main end-product of dopamine metabolism.

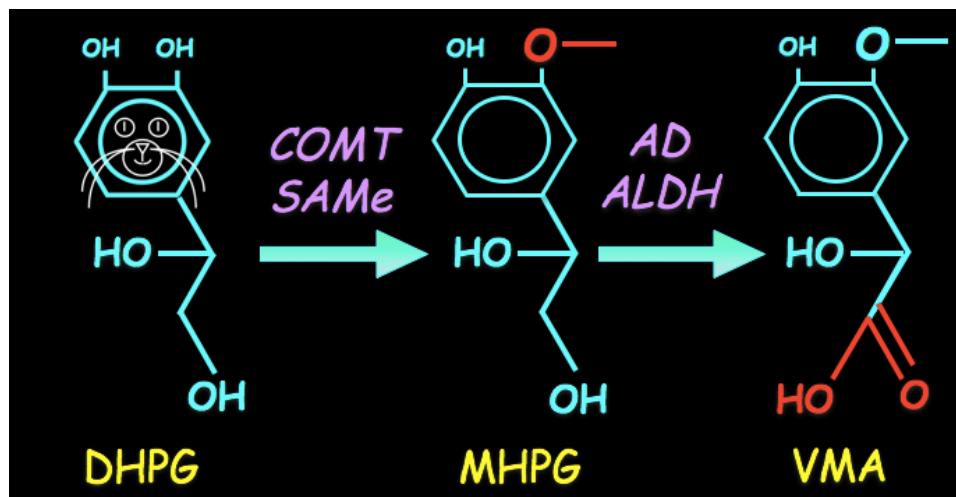


DOPAC is converted to HVA by the enzyme COMT.

HVA is the main end-product of dopamine metabolism in the body.

Both MHPG and VMA are major end-products of norepinephrine metabolism. DHPG is converted to MHPG by COMT. In the liver, MHPG is converted to VMA.

Ingesting alcohol (ethanol) competes with MHPG for alcohol dehydrogenase (AD) in the liver, and this increases the amount of MHPG with respect to VMA.



MHPG and VMA are end-products of norepinephrine metabolism. In the liver, MHPG is converted to VMA via alcohol dehydrogenase (AD) and aldehyde dehydrogenase (ALDH).

Summary of Catecholamine Synthesis & Metabolism

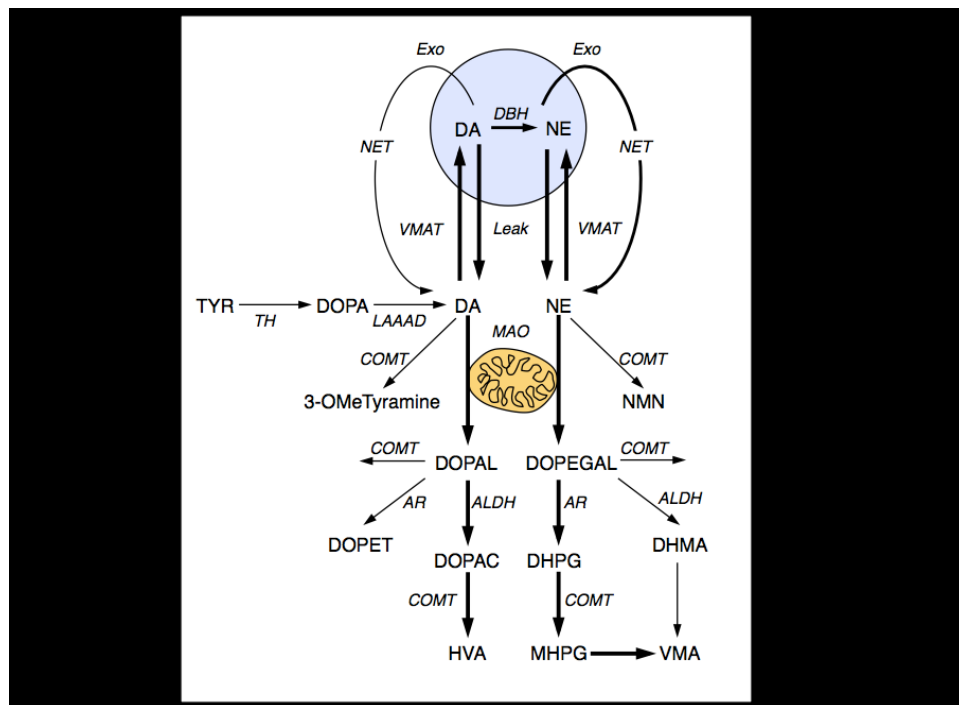
Here is a summary diagram of norepinephrine synthesis and metabolism. There are a few general principles to keep in mind.

First, dopamine and norepinephrine have a single source, DOPA.

Second, dopamine is made in the cytoplasm, whereas norepinephrine is made in the vesicles.

Third, released norepinephrine is recycled by uptake into the cytoplasm via the NET and uptake into the vesicles via the

VMAT.



Overview of catecholamine synthesis and metabolism.

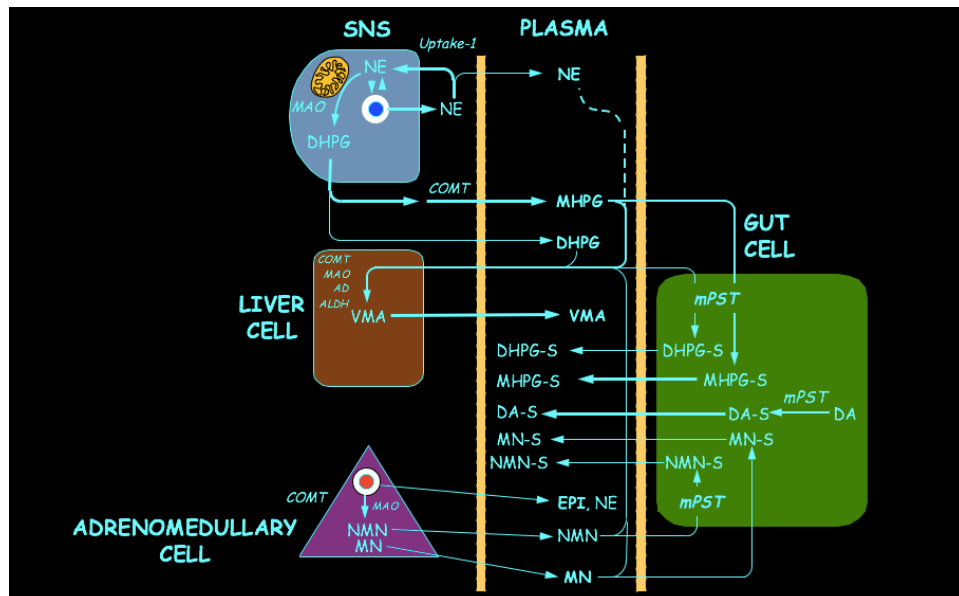
Fourth, in healthy people, the main determinant of catecholamine turnover is not release by exocytosis followed by extra-neuronal metabolism but vesicular leakage followed by MAO.

Fifth, as depicted in the diagram above, MAO plays a central role in catecholamine metabolism. Virtually all of neuronal catecholamine metabolism occurs via MAO.

Finally, end-products of catecholamine metabolism are formed in the gut and liver.

The plasma of healthy people contains an abundance of

catechols and catecholamine metabolites. Even the complex overview in the diagram below probably doesn't include other related compounds that have particular meanings in terms of functions of catecholamine systems in the body.

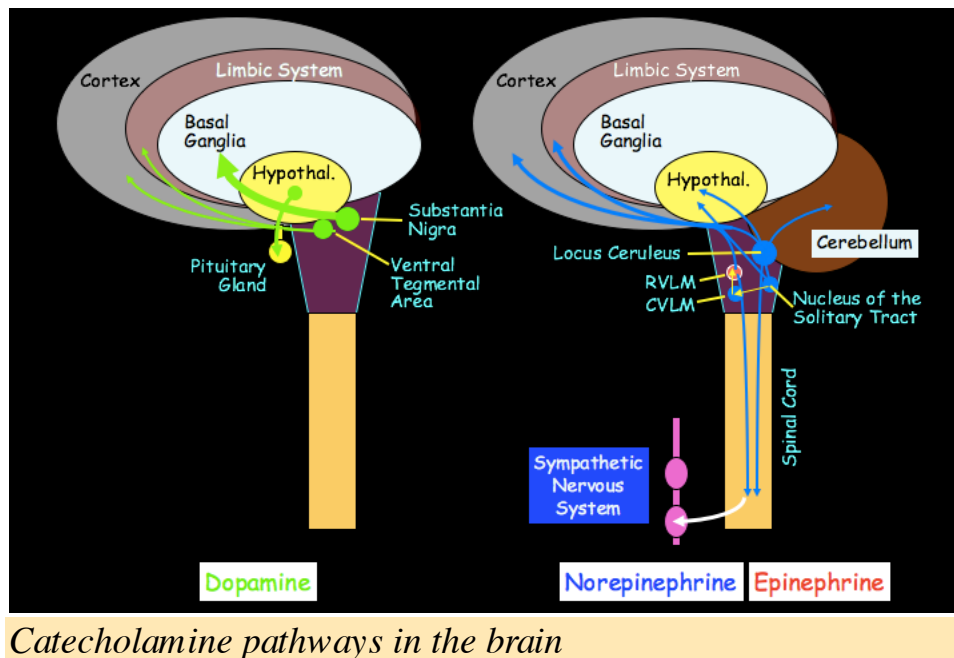


Overview of plasma catecholamines and their metabolites. The levels are determined complexly and involve sympathetic nerves, adrenomedullary cells, the liver, and the gut.

Catecholamine Systems in the Brain

Catecholamine in the brain are found in two norepinephrine and three dopamine pathways and in specific clusters of brainstem and hypothalamic neurons.

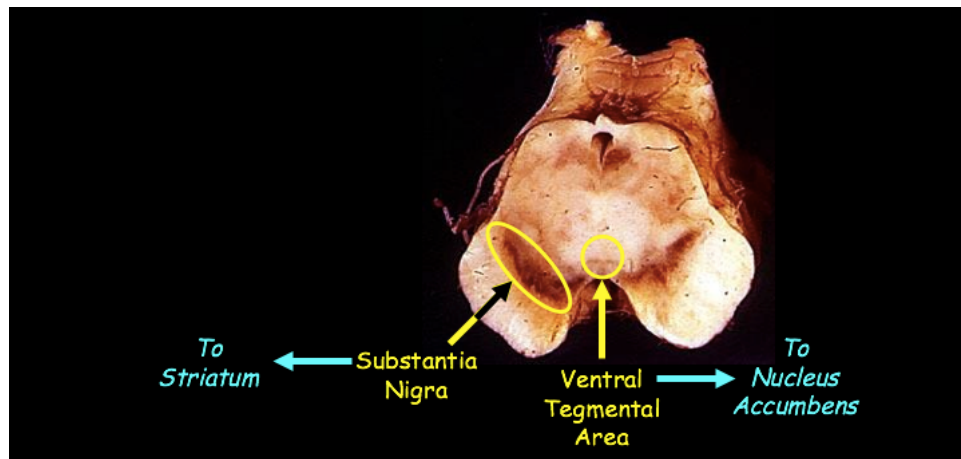
Several different functions of dopamine have been proposed in its three chemical pathways. The nigrostriatal system is the main source of dopamine in the brain and the main determinant of dopamine effects on movement.



Patients with Parkinson's disease experience particular difficulty with "pill-roll" tremor at rest and with initiating and terminating movements, presumably because of nigrostriatal dopamine deficiency. The nigrostriatal system courses from pigmented cells in the substantia nigra ("black substance") in the midbrain portion of the brainstem to much larger structures toward the middle front of the brain. These structures are collectively called the "basal ganglia."

The nomenclature for the components of the basal ganglia is confusing. The basal ganglia include the caudate ("tail-like") nucleus and lenticular ("lens-like") nucleus. The lenticular nucleus, in turn, consists of the putamen and globus pallidus. The corpus striatum, often simply called the striatum, consists of the caudate and putamen. One would think the striatum and globus pallidus would be synonymous with the basal ganglia, but some authorities include other components in the basal

ganglia.



Midbrain dopaminergic neurons are in the substantia nigra and ventral tegmental area.

The mesolimbic (or mesocortical, or mesolimbocortical) system sends dopamine fibers from the ventral tegmental area in the midbrain to the nucleus accumbens and then to other parts of the limbic system, such as the hippocampus and amygdala, and to parts of the cortex, such as the anterior cingulate cortex and pre-frontal cortex. It is thought that this system is dysfunctional in schizophrenia, because many effective drugs for schizophrenia appear to work by blocking the effects of dopamine released in this system. In the mesolimbic system, dopamine seems to increase locomotion and positive reinforcement, not so much due to pleasurable reward sensations as due to an enabling action that decreases the threshold for initiating responses. Predictably, functional alterations of the mesolimbic system are associated with all known forms of addiction.

Finally, the tuberoinfundibular (or tuberohypophyseal) system

delivers dopamine from cells in the hypothalamus to the pituitary gland. Dopamine in the pituitary gland inhibits production of prolactin. In postpartum women who don't want to breast-feed, a single injection of bromocriptine, which stimulates dopamine receptors, prevents lactation.

Complete destruction of all dopamine systems in the brain produces a syndrome of decreased movement, inattention, decreased food intake, and decreased fluid intake; it gives the appearance of generalized behavioral unresponsiveness. This “dopamine deficiency syndrome” applies to all voluntary acts requiring motivation, sustained alertness, and receptiveness to sensory input. Animals deficient in dopamine fail to initiate coordinated movements and fail to orient to sensory stimuli. Motivated behaviors are not eliminated, but the arousal threshold appears to be increased before the behaviors are elicited. Most of the research in this area has depended on administration of a neurotoxin to produce chemical destruction of dopamine cells and terminals; however, the same neurotoxin also destroys norepinephrine cells and terminals.

Conversely, increased occupation of dopamine receptors in the brain, such as produced by DOPA, amphetamines, or drugs that stimulate dopamine receptors directly, produces hyperactivity, stereotyped involuntary movements, agitation, psychosis, and risk taking. Patients with Parkinson's disease who take dopamine receptor stimulants can have a surprisingly high frequency of an unusual but related side effect—gambling.

Norepinephrine also is an established neurotransmitter in the brain, although little is known about what it does exactly in humans. Based on studies in animals, norepinephrine, rather

than acting as a direct inhibitor or stimulator of neuronal function, seems mainly to modify responsiveness to other inputs. Activation of the locus ceruleus, the brainstem source of most of the norepinephrine in the brain, biases attention toward novel, rapidly changing signals from sense organs monitoring both the outside and inner worlds. Norepinephrine in the locus ceruleus system may therefore play a role in vigilance behavior and in registration of distressing events in long-term memory.

A descending pathway from brainstem norepinephrine-producing neurons down the spinal cord seems to contribute to “stress-induced analgesia.” If you’ve ever played in an athletic competition involving repeated bouts of running and noticed painful foot blisters after the game is over, you know what stress-induced analgesia is.

Lower in the brainstem, norepinephrine-producing cells participate in neurocirculatory reflexes. Most of the evidence for such a role comes from studies of the baroreflex in laboratory animals. For instance, norepinephrine-producing cells exist at high concentration in the nucleus of the solitary tract (NTS). The NTS is the main site of termination of input from the baroreceptors to the brain. From the NTS, nerve fibers branch widely as they ascend to higher levels of the central nervous system, such as the hypothalamus and amygdala. Conversely, as part of coordinated behavioral, emotional, and autonomic nervous system responses, descending pathway traffic in fibers from higher centers to the NTS can “reset the barostat” and redefine “normal” blood pressure. A loss of norepinephrine-producing cells in the NTS can help explain why some neurodegenerative diseases feature extreme swings

of blood pressure.

Despite the fact that both dopamine and norepinephrine are known neurotransmitters in the brain, and despite the apparent involvement of dopamine systems and norepinephrine systems in responses to a variety of environmental and internal inputs, interactions between dopamine systems and norepinephrine systems have received remarkably little research attention, especially in humans.

The rostral ventrolateral medulla (RVLM) includes neurons called C1 neurons that contain the enzyme PNMT. PNMT catalyzes the conversion of norepinephrine to adrenaline, and C1 neurons are thought to be adrenergic. RVLM neurons are a major source of descending projections to the sympathetic pre-ganglionic neurons in the intermediolateral columns of the spinal cord. They also project rostrally to the paraventricular nucleus of the hypothalamus. According to one view, the C1 neurons are the “body’s EMTs” because of their involvement with emergency responses to pain, infection, blood loss, hypoxia, and hypoglycemia—analogous to the sympathetic adrenergic system in the periphery.

RECEPTORS

The main chemical messengers of the autonomic nervous system are acetylcholine and the catecholamines norepinephrine and epinephrine. Acetylcholine and norepinephrine are neurotransmitters, whereas epinephrine is a hormone.

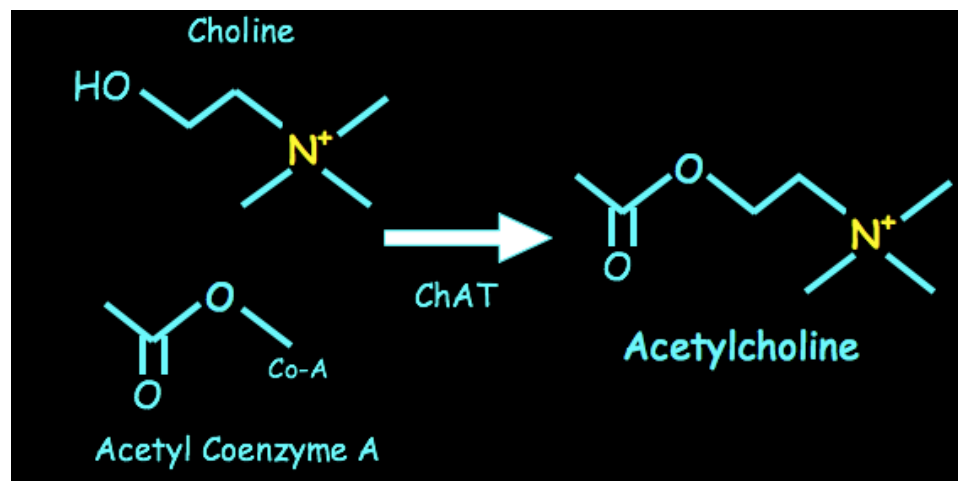
All the chemical messengers of the autonomic nervous system exert their effects on body functions by receptors.

Receptors are highly specialized molecules embedded in the membranes of the target cells such as heart muscle cells.

The synthesis of these chemical messengers and the processes of their metabolism seem relatively simple compared to the bewildering arrays and locations of the receptors.

Most drugs used to treat dysautonomias work by way of their effects on receptors.

Mushrooms and Tobacco



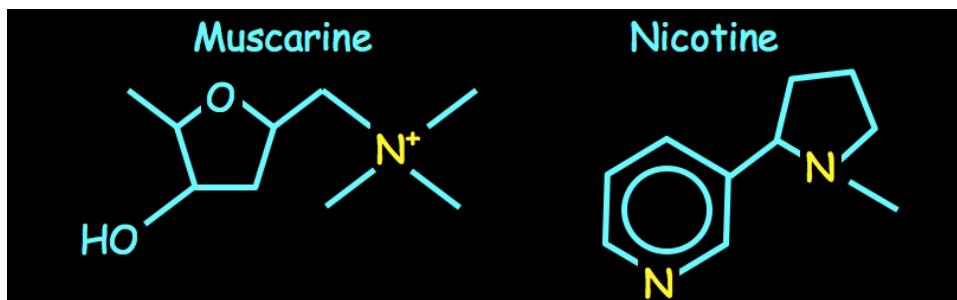
Acetylcholine synthesis

Acetylcholine is produced from the action of an enzyme,

choline acetyltransferase (ChAT), on choline and acetyl coenzyme A in the cytoplasm. The enzyme catalyzes the transfer of the acetate ion to choline. The acetylcholine (ACh) is then actively taken up into vesicles by a transporter (the vesicular acetylcholine transporter, or VACHT).

After release of acetylcholine by exocytosis into the extracellular fluid, the transmitter can bind to specific receptors on target cells. Acetylcholine is also rapidly broken down by the enzyme acetylcholinesterase (AChE), which regenerates the acetate and choline. Because of the rapid breakdown of acetylcholine by AChE, it is impossible to monitor activity of the cholinergic neurons by measuring levels of acetylcholine in body fluids such as plasma or urine; but some the effects of stimulation or blockade of muscarinic receptors are obvious.

The history of acetylcholine receptors begins with John Newport Langley, the same Langley who coined the terms “autonomic nervous system” and “parasympathetic nervous system.” In 1905 Langley proposed that skeletal muscle expresses “a substance that combines with nicotine and curare...receives the stimulus and transmits it.” He referred to a “receptive substance” in the muscle.

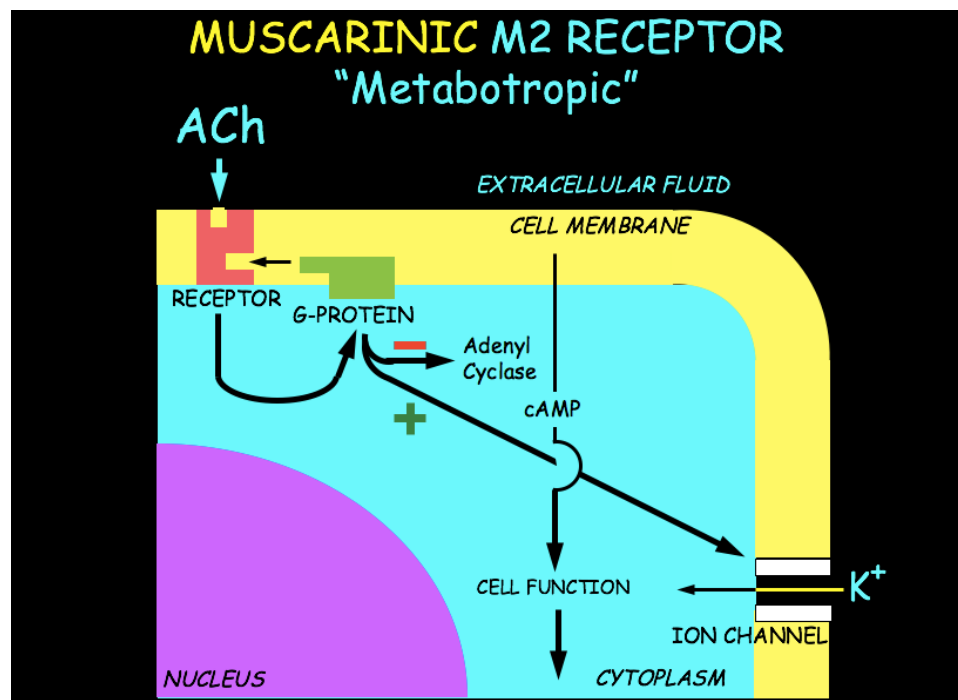


Chemical structures of muscarine and nicotine

There are two classes of receptors for acetylcholine—muscarinic and nicotinic. These names are derived from the drugs muscarine, made in certain types of mushrooms, and nicotine, made in tobacco plants.

Inspection of the chemical structures of muscarine and nicotine show similarities. They are both small organic molecules that contain prominent nitrogen atoms—just like the catecholamines do.

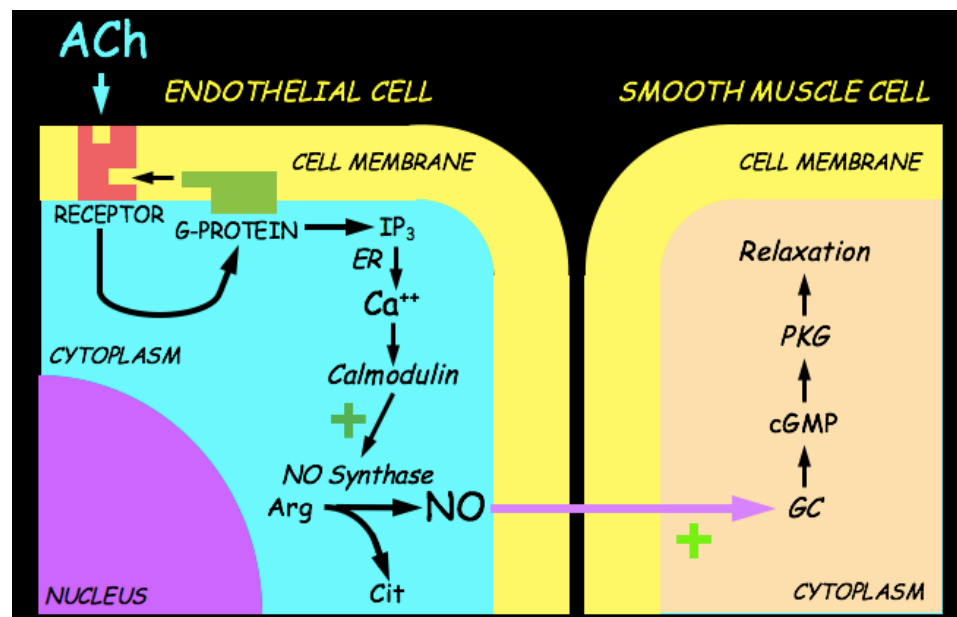
Muscarinic receptors are expressed in virtually all the organs of the body, including the heart, gut, sweat glands, urinary bladder, and lungs. Probably the most noticeable effect of muscarinic receptor stimulation is gastrointestinal upset, with nausea and vomiting.



Muscarinic receptors are called “metabotropic,” because they alter cell function via production of second messengers.

There are 5 different types of muscarinic receptors. The M2 form is the main form in the heart. Stimulation of M2 receptors in the heart decreases the rate and force of heart contraction, via two processes. First, stimulation of M2 receptors on the heart muscle cells inhibits the cells' activities via decreasing generation of the second messenger cyclic AMP and increasing entry of potassium ion into the cells. Second, stimulation of M2 receptors on cardiac sympathetic nerves inhibits norepinephrine release for a given amount of post-ganglionic sympathetic nerve traffic.

Another cholinergic signaling system that mediates relaxation of blood vessels independently of muscarinic receptors involves production of the gas, nitric oxide (NO).

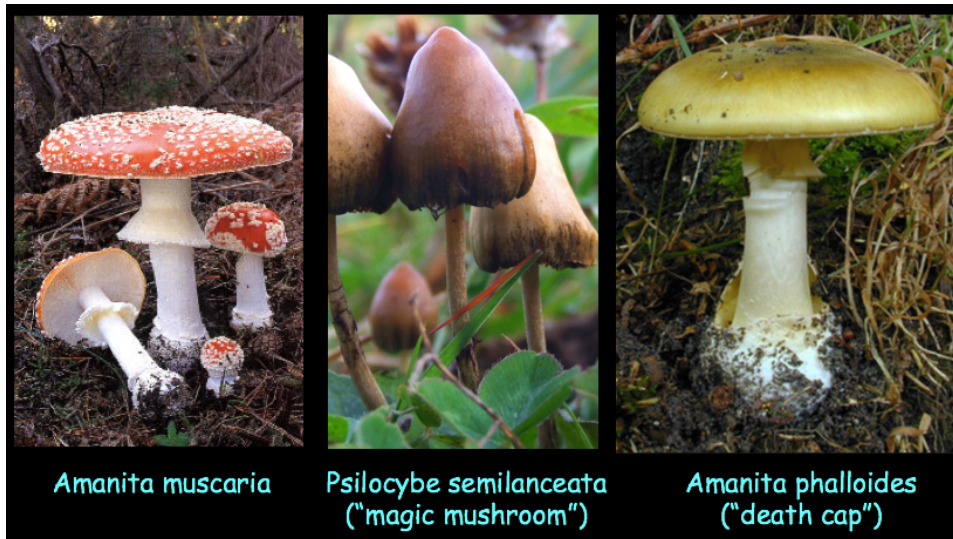


The NO signaling system mediates vascular smooth muscle relaxation in response to acetylcholine.

NO is generated in different types of cells. In this case we are dealing with NO production within the endothelial cells that line the innermost walls of blood vessels. NO diffuses from the endothelial cells to nearby smooth muscle cells, causing the smooth muscle cells to relax. The acetylcholine/NO mechanism plays an important role in the relaxation of local blood vessels in the corpora cavernosa that enables blood to engorge the penis during erection. When this pair of sponge-like structures fill with blood, the dilation interferes with venous return of blood in the shaft, and the penis stiffens.

MAGIC MUSHROOMS 101

When I was a junior resident in internal medicine in Seattle, one night when I was working in an emergency room a group of students came in, all looking acutely ill. They had ingested what they thought were psychedelic (psilocybin) mushrooms.



Some mushrooms relevant to the autonomic nervous system.

It hadn't take long before they'd realized they'd made a bad mistake. All were retching and vomiting, and in the vomitus were some mushroom parts.

A chemical found in some mushrooms was the basis for naming one class of acetylcholine receptors — muscarinic.

At the time, on the faculty of the University of Washington was Dr. Daniel Stuntz, a professor of botany who was a renowned authority on mushrooms. We called him up, and he came to the emergency room. I remember him looking stereotypically professorial in his cardigan sweater, which contrasted with our medical white jackets.

He identified the matter in the students' vomitus as from a variety of poisonous mushroom called *amanita phalloides*, also known somewhat more graphically as “death cap.” The retching and vomiting in these students came from muscarinic toxicity.

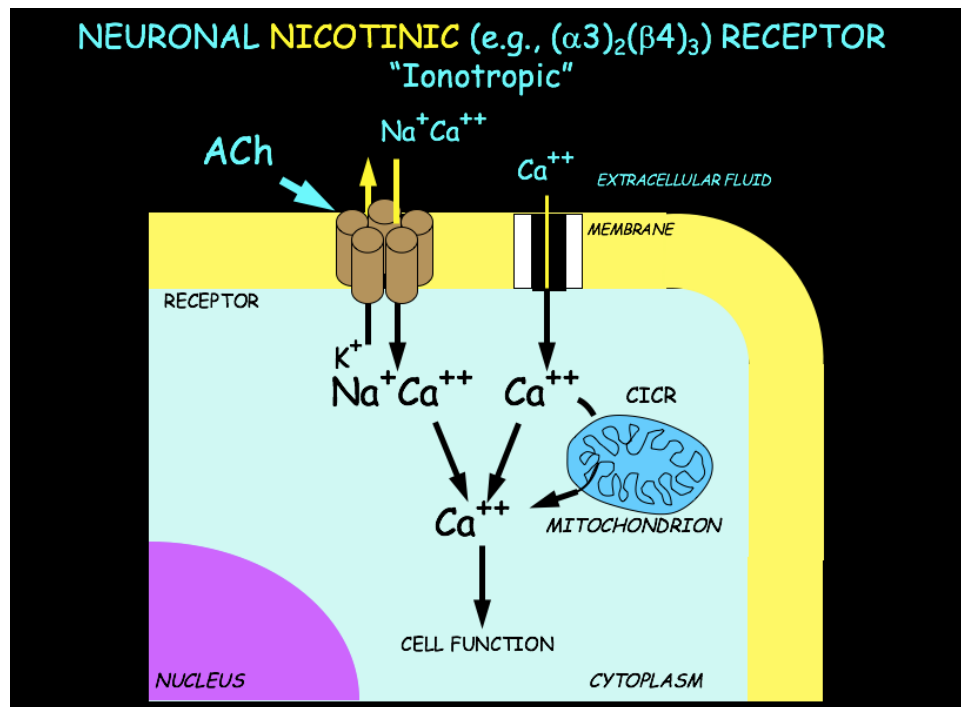
Dr. Stuntz truly was an expert on the subject. Several years previously he had discovered a new species of the psychedelic mushroom *Psilocybe* on the UW campus. This species was later named *Psilocybe stuntzii* in his honor.

IT'S A GIRL!

Nicotine is the classic stimulator of the neuronal nicotinic receptor—the first type of neurotransmitter receptor to be

identified.

There are numerous types and sub-types of nicotinic receptors. All have 5 component parts—i.e., they are pentamers. For instance, a common arrangement in the sympathetic ganglia is a pentamer that has 2 alpha-3 subunits and 3 beta-4 subunits.



Nicotinic receptors are ionotropic, because they stimulate the cell by building up ions in the cytoplasm.

Nicotinic receptors are called "ionotropic," because when occupied by acetylcholine they let ions in from the extracellular fluid. By letting in sodium ions the cells lose some of their charge (i.e., they depolarize), and the depolarization lets in calcium ion. Calcium ion builds up in the cell through the channel itself or via induced calcium release from intracellular stores. It is the buildup of ionized calcium in the cytoplasm that

activates the cell. In particular, stimulation of nicotinic receptors on adrenal medullary cells rapidly evokes adrenaline release.

When my brother and sister-in-law had their youngest daughter, they gave me an “It’s a Girl!” cigar. I never have been a tobacco smoker, but given the occasion I thought I should smoke it. My wife wouldn’t let me smoke in the house, so I decided to take a leisurely stroll in the neighborhood around our long block. I lit up and started my walk, and I was puffing away proudly with my chin high and hands clasped behind my back, when about half way around the block I suddenly came to the realization I was about to die.

In non-smokers, the nicotine in tobacco smoke releases adrenaline, producing fast pulse rate, sweating, pallor, hyperventilation, and a “feeling of impending doom.”

My heart was racing, I broke out in a sweat, I gasped for breath, I began to tremble, and, tellingly, I experienced what in medical circles is called the “feeling of impending doom.” I made it home and flung myself on the couch in our family room. From my pallor, sweating, hyperventilation, and tremulous speech, everyone was immediately concerned and wanted to know what was wrong. I gasped, “It’s that damned It’s a Girl! cigar.” All my symptoms and signs were due to adrenaline, released by my adrenal glands upon occupation of nicotinic receptors on my adrenomedullary cells.

PRETTY WOMAN

Blockade of effects of the parasympathetic nervous system on the pupils causes the pupils to dilate.

According to tradition, Italian women used to instill in their eyes a product of the root of a plant in the genus *Atropa*, out of the belief that the drug-induced dilation of the pupils would make them more attractive. The extract came to be called “belladonna,” meaning “pretty woman.” In fact, the full taxonomic name of the plant is *Atropa belladonna*.



Atropine, derived from the plant, Atropa belladonna, dilates the pupils.

A less appealing appellation for the same plant is “deadly nightshade.” Every part of the plant is poisonous, and atropine overdose can be lethal. Atropine overdose manifests with dry mouth, dry eyes, pupillary dilation, lack of sweating, lack of gastrointestinal and urinary bladder tone, rapid heart rate, delirium, and coma. The word, *Atropa*, is derived from the

Atropos, one of the Fates in Greek mythology. *Atropos* held the shears that could cut the thread of human life.

Troops at risk of exposure to organophosphorus nerve gases such as sarin are issued atropine auto-injectors. By blocking muscarinic receptors atropine can interfere with toxic effects of nerve gas-induced blockade of acetylcholinesterase (AChE). AChE blockade floods cholinergic receptors and causes death by asphyxia due to inability to regulate respiratory muscles.

During the 1991 Persian Gulf war, precipitated by Saddam Hussein's Iraqi troops invading Kuwait, scud missiles were fired on civilian neighborhoods in Tel Aviv. Many of the casualties were people who had injected atropine into themselves for what they thought was a nerve gas attack.

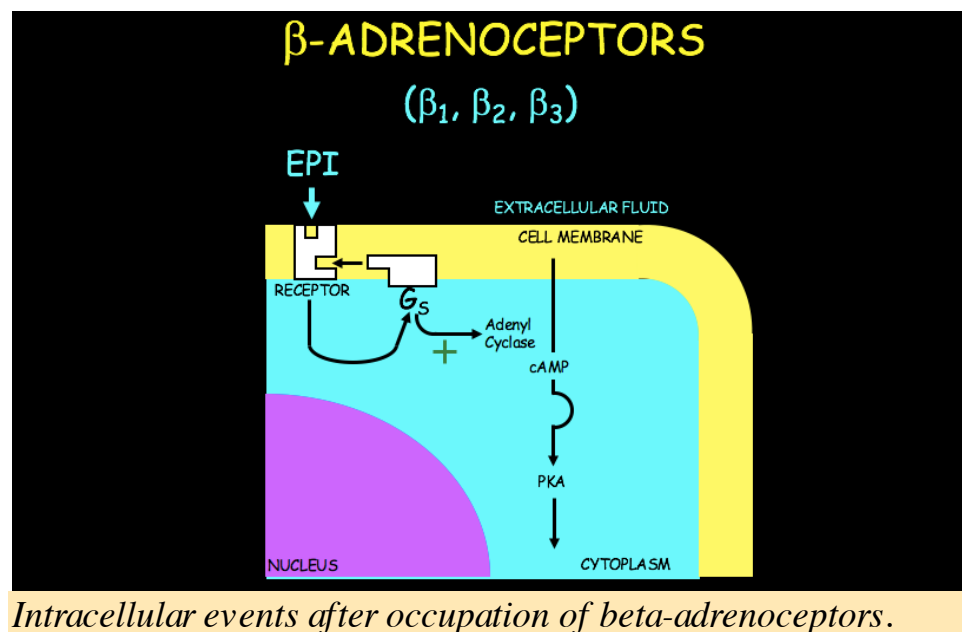
"FIRST I SECRETED A HELL OF A LOT OF ADRENALINE"

About the same time that U.S. von Euler identified norepinephrine as the neurotransmitter of the sympathetic nervous system (disproving Cannon's notion about adrenaline being the sympathetic neurotransmitter), Raymond P. Ahlquist proposed an explanation for the impressively large variety of effects of the two rather simple chemicals.

Ahlquist's idea was that catecholamines differentially stimulate specific receptors—adrenergic receptors or adrenoceptors. In 1948, he suggested that there were two types of adrenoceptors, alpha and beta.

Norepinephrine would stimulate alpha adrenoceptors, the synthetic catecholamine isoproterenol would stimulate beta adrenoceptors, and adrenaline would stimulate both types of adrenoceptors.

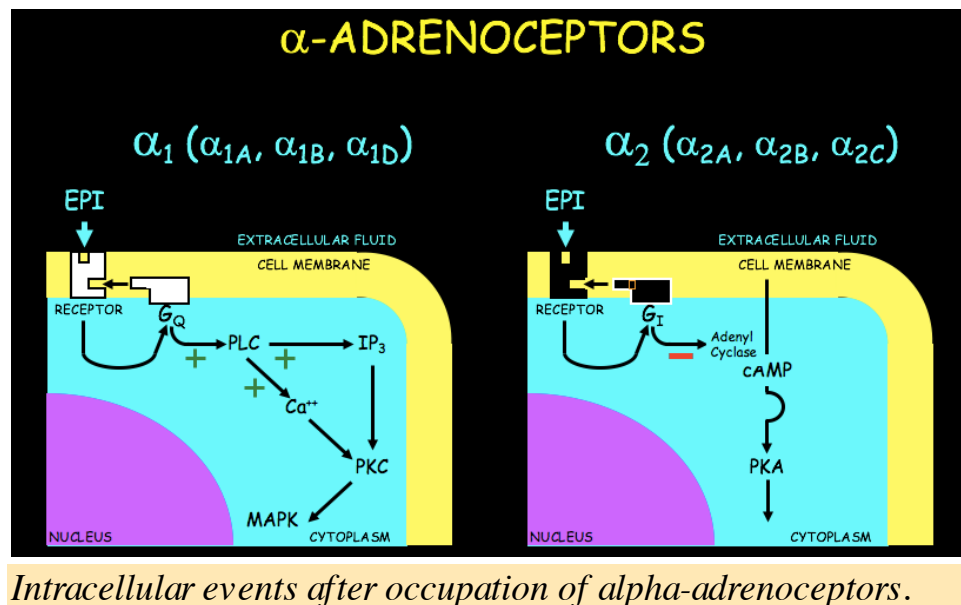
Numerous studies, using drugs and more recently molecular genetic tools, have by now not only confirmed Ahlquist's suggestion but actually provided the molecular structures of adrenoceptors.



The discovery of adrenoceptors led to the development of novel, highly successful drugs to treat many common and important disorders, such as hypertension, abnormal heart rhythms, coronary artery disease, and heart failure. For the development of beta-adrenoceptor blockers, which remain key agents in the treatment of hypertension, angina pectoris, and abnormal heart rhythms, Sir James Black shared the Nobel Prize for Physiology or Medicine in 1988. For cloning the

genes encoding beta-adrenoceptors and thereby elucidating their molecular structures, Brian Kobilka shared a Nobel Prize for Chemistry in 2012.

There are 9 different adrenoceptors in humans— α_1A , α_1B , α_1D , α_2A , α_2B , α_2C , β_1 , β_2 , and β_3 .



Adrenoceptors such as beta adrenoceptors in the cell membrane transmit information via specific “G-proteins” (the “G” standing for guanine-nucleotide-regulatory proteins). The G-proteins are located near the receptors on the inner portion of the cell membrane. For the discovery of G-proteins and their significance in cellular activation by adrenaline, Alfred G. Gilman and Martin Rodbell shared the Nobel Prize in Physiology or Medicine in 1994.

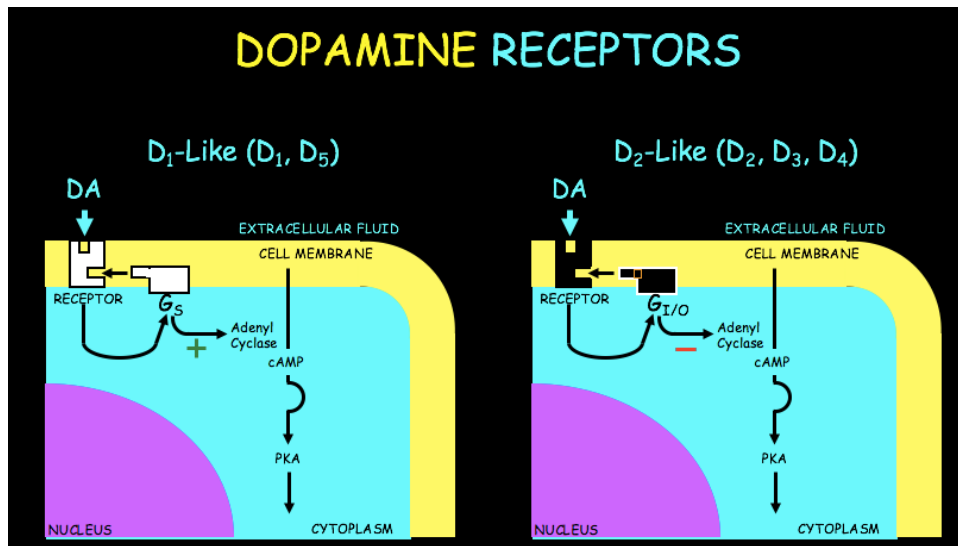
Describing to an audience of colleagues his reaction to the news that he had won a Nobel Prize, as reported in the Washington Post, Gilman quipped, “First, I secreted a hell of a lot of

adrenaline and then that reached my adrenergic receptors and they responded via the G-proteins.”

In the liver, adrenaline liberates the vital metabolic fuel, glucose. This is a major way that adrenaline increases blood glucose levels. The release of glucose by adrenaline takes place partly by stimulating the breakdown of glycogen to form glucose in the liver. The breakdown of glycogen, in turn, involves a rather involved cascade of biochemical events. For this cascade to begin requires formation of a messenger substance inside the cells, cyclic adenosine monophosphate (cAMP). The discovery of cAMP, the first identified intracellular messenger (“second messenger,” the first being the hormone itself, in this case adrenaline), depended on studies of the fractions of cell homogenates that were required for the hormonal effects of adrenaline and another hormone, glucagon, in the liver. For the discovery of cAMP, E. W. Sutherland received a Nobel Prize in 1971.

A family of chemicals called arrestins help turn off the intracellular cascade that activates cells when G-protein-coupled receptors such as beta-adrenoceptors are occupied. Beta-arrestin was one of the first arrestins to be identified (“beta” because this form of arrestin is associated with beta-adrenoceptors). The first step in the desensitization of the receptors is phosphorylation by a class of chemicals called G-protein coupled receptor kinases (GRKs). The action of a GRK prepares the receptor for binding to arrestin. The arrestin binding to the receptor then blocks further G-protein-mediated signaling and also targets the receptors for displacement from the cell membrane into the cytoplasm. For the discovery of beta-arrestin, Robert Lefkowitz shared a Nobel Prize in 2012.

Medical textbooks often include imposing-looking charts that list the numerous types and subtypes of adrenoceptors and dopamine receptors. The remarkable array of receptors contrasts starkly with the small family of chemicals that reach those receptors. The multiplicity of receptors for



Intracellular events after occupation of dopamine receptors.

catecholamines generally fits with the notion that natural selection has favored the evolution of multiple effectors.

FRAU SCHWANDT'S COLD

In the early 1960s, chemists at the German drug company Boehringer-Ingelheim came up with what they thought would be an effective treatment for nasal congestion.

The drug, clonidine, which has an imidazoline chemical structure, constricted blood vessels in a manner similar to phenylephrine, the alpha-1 adrenoceptor agonist sold as

NeoSynephrine™, but clonidine had a longer duration of vasoconstrictor action.

In 1962, the secretary to the medical director, a Frau Schwandt, came down with a bad cold, and the medical director applied a dilute solution of clonidine to the mucus membranes of her nose. Soon after, she fell asleep, and she didn't wake up until the next day.

Her blood pressure and heart rate also fell substantially. It was soon realized that clonidine enters the central nervous system, producing sedation and dropping sympathetic noradrenergic system outflows to the blood vessels and heart. The company creatively redirected its marketing strategy, and the drug was developed and is still marketed (as Catapres™) for treating hypertension. The drug has also been used successfully to treat conditions as diverse as alcohol and opiate withdrawal, baroreflex failure, and attention deficit hyperactivity disorder.

It is thought that in humans clonidine works in humans by stimulating both alpha-2 adrenoceptors and imidazoline receptors.

Ironically, the active ingredient in NeoSynephrine™ 12-hour nose spray is no longer phenylephrine but oxymetazoline, another imidazoline like clonidine but one that does not readily enter the brain.

HOMEOSTASIS, STRESS, and DISTRESS

Homeostasis

BERNARD AND THE "INNER WORLD"

Understanding of the roles of the autonomic nervous system in health and disease begins with the teachings and demonstrations of Claude Bernard.

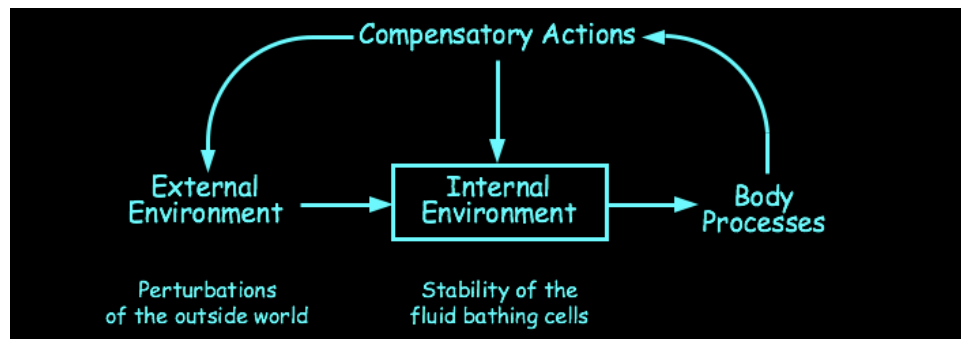


Claude Bernard, father of the milieu intérieur, the internal environment.

Bernard introduced the idea of the “inner world” inside the body when he theorized that body systems function to maintain a constant fluid environment bathing the cells—what he called the *milieu intérieur*.

Bernard's conception evolved over several years. Near the end of his life, in about 1876, he postulated that the body maintains

the constant internal environment by myriad, continual, compensatory reactions. These compensatory reactions tend to restore a state of equilibrium in response to any outside changes. They enable independence from the external environment.



Claude Bernard taught that compensatory actions help maintain the internal environment.

Bernard therefore not only introduced the notion of an apparently constant inner world but also a purpose for body processes. He wrote, “The constancy of the internal environment is the condition for free and independent life...All the vital mechanisms, however varied they might be, always have one purpose, that of maintaining the integrity of the conditions of life within the internal environment.” This view may seem obvious now, but it was revolutionary in the history of medical ideas.

Bernard’s visionary concept of the stability of the internal environment attracted little attention until the Walter B. Cannon’s classic 1926 review in which Cannon introduced the theory of homeostasis.

CANNON'S "HOMEOSTASIS"

Walter B. Cannon invented the term, “homeostasis,” to describe the stability of various constituents of body fluids and of core temperature. The full description of this new concept was based on the results of Cannon’s own studies and those reported in the two decades preceding his 1929 review, “Organization for Physiological Homeostasis.”

In that review he acknowledged the importance of Bernard’s “fixity of the *milieu intérieur*” and quoted Haldane’s comment, “No more pregnant sentence was ever framed by a physiologist.”

Cannon recognized the role of the brain in coordinating body systems to keep values for key internal variables within bounds in the event of internal or external disturbances. These threats to homeostasis, by causing sensed deviations from the goal values, arouse internal nervous and hormonal systems, induce reflexive physiological changes, produce externally observable behaviors, and prompt internal emotional and motivational states, all of which serve to preserve homeostasis. Unlike a state of equilibrium that does not require energy (e.g., stability of blood acidity via the bicarbonate buffering system), homeostasis is energy-requiring.

Walter B. Cannon invented the word, “homeostasis.” By this term he was referring to the stability of the inner world of the body. Energy-requiring processes are required for that stability.

According to Cannon, core temperature, blood levels of oxygen and glucose, concentrations of red blood cells in the bloodstream, amounts of electrolytes, and many more “variables” of the body normally don’t vary by much; they are kept within ranges.

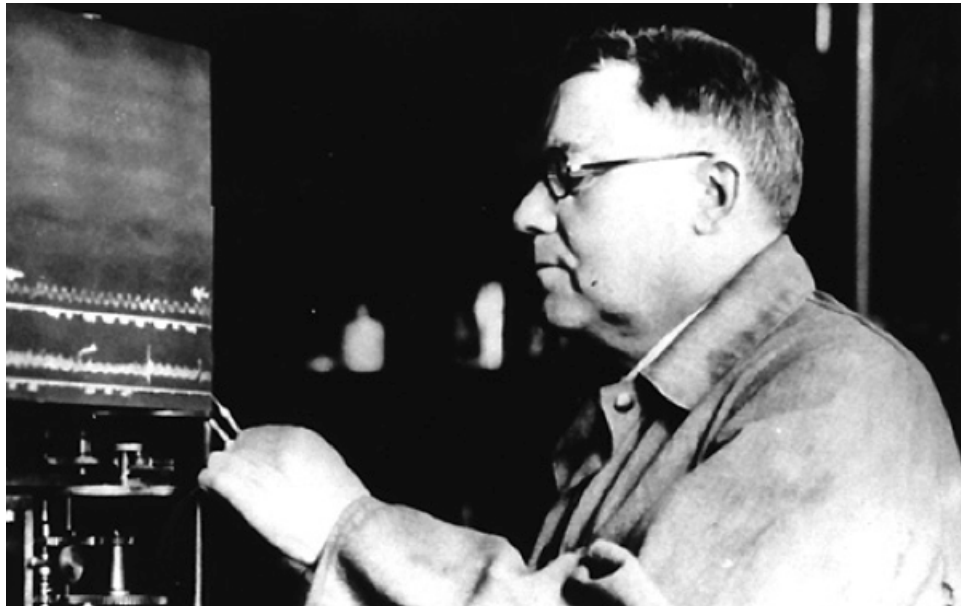
Interestingly, Cannon never referred to homeostasis of blood pressure, even though this has become a focus of research and practice in autonomic medicine.

Walter B. Cannon taught that the body responds to all emergencies in the same way, by evoking increased secretion of adrenaline.

In higher organisms, maintaining homeostasis depends on complex coordination by the brain. Just as the brain receives information from sense organs about and determines our interactions with the outside world, the brain also receives information from internal sensors and acts on that information to regulate the inner world. For most of our lives the brain tracks many monitored variables by way of internal sensory information and acts on that information to maintain levels of monitored variables by modulating numerous effectors that work in parallel.

Later you will learn much more about how hierarchies of nerve networks in the central nervous system mediate this regulation. In his 1929 review Cannon hinted at this when he wrote the following about temperature homeostasis: “The delicate thermostat...appears to be located in the subthalamus and to be influenced directly by changes in the temperature of the blood

and also reflexly. The noteworthy features of the total arrangement, apart from its efficiency, are the varieties of the devices for homeostasis, their appearance in a sequence of defences against change, and the close involvement of the sympathetic system in the conservation, production and dissipation of heat.” Thus, nearly 100 years ago a basic understanding was emerging that brain centers mediate a variety of homeostatic reflexive changes.



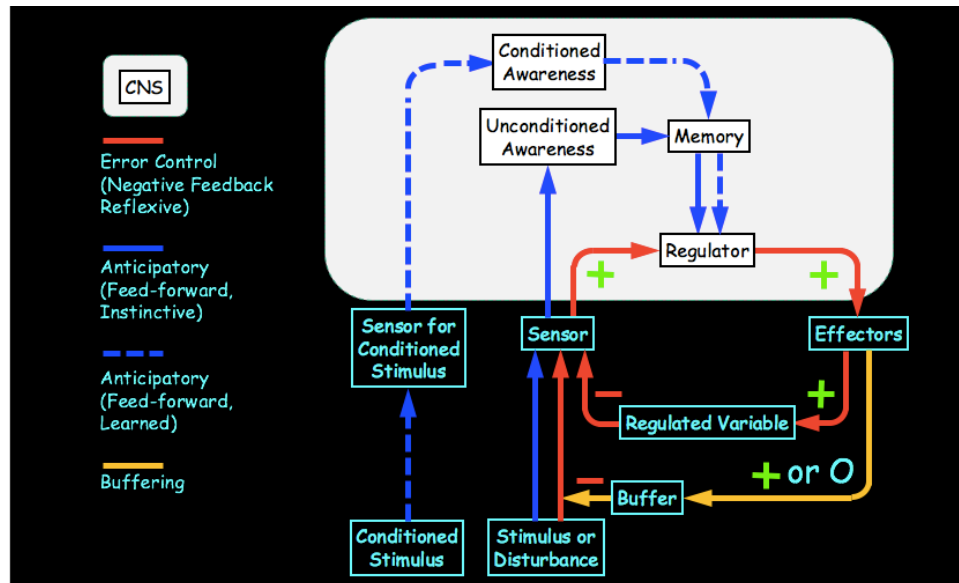
Walter B. Cannon, who coined the word, “homeostasis.”

Cannon was unabashedly teleological in his viewpoint. He wrote, “My first article of belief is based on the observation, almost universally confirmed in present knowledge, that what happens in our bodies is directed toward a useful end.”

THREE ROUTES TO HOMEOSTASIS

It has been proposed that three types of process maintain homeostasis. The first and most well known is error control by negative feedback regulation. The second is feed-forward regulation, which is the most challenging from a theoretical point of view.

The third, which seems not to have been incorporated explicitly previously in concepts of homeostasis, is buffering.



Three mechanisms of homeostasis— error control (negative feedback), anticipatory (feed-forward), and buffering. Anticipatory regulation can be instinctive or learned.

The Figure above shows the relationships of reflexive error control via negative feedback (red), buffering (tan), and anticipatory regulation (blue). The anticipatory control mechanisms can be instinctive (solid lines) or conditioned

(dashed lines). A disturbance can arouse anticipatory instinctive responses by pathways involving awareness (conscious or unconscious); and an associated conditioned stimulus can arouse anticipatory responses by pathways involving awareness and conditioned learning. A disturbance is sensed by interoceptors (e.g., gastrointestinal hemorrhage) or exteroceptors (e.g., touching a hot iron), while a conditioned stimulus is sensed by exteroceptors.

Behavioral responses to buffer the cold include huddling, seeking shelter, hibernation, and bird migration. Humans can also don appropriate clothing, which is inserting a buffer. Thus, buffering can be energy-dependent or energy-independent. In the Figure, the + or 0 refers to buffering dependent on or independent of effector activation.

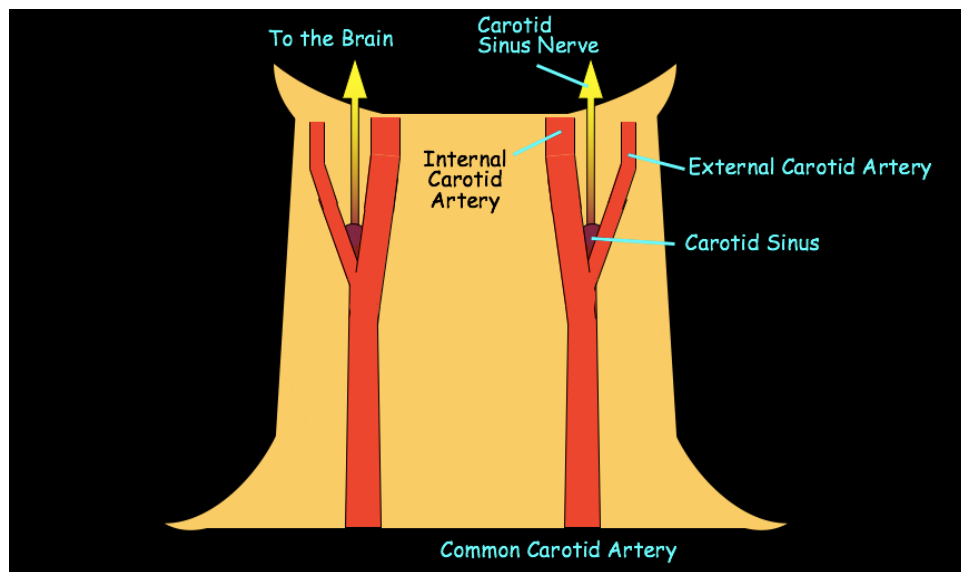
The Sleeper Hold

My grandmother and I used to watch professional wrestling on TV. Propped in bed, she would cheer on her hero, Antonino Rocca, the barefoot master of the flying dropkick, and scold Skull Murphy, who was notorious for butting opponents senseless with his shaved, vaselined head.

In professional wrestling you can win by three smacks by the referee on the tarp, by disqualification, or by submission. In particular, in the “sleeper hold,” the attacker suddenly and unexpectedly circles the victim and wraps arms around the victim’s neck, as if to choke from behind; but instead of choking the victim, the attacker massages both sides of the opponent’s neck vigorously below the angles of the jaw. After

several seconds of this massaging, the opponent slumps to the mat unconscious; that ends the bout.

Over the years I came to question the veracity of professional wrestling, but I do think there is a kernel of truth to the sleeper hold.

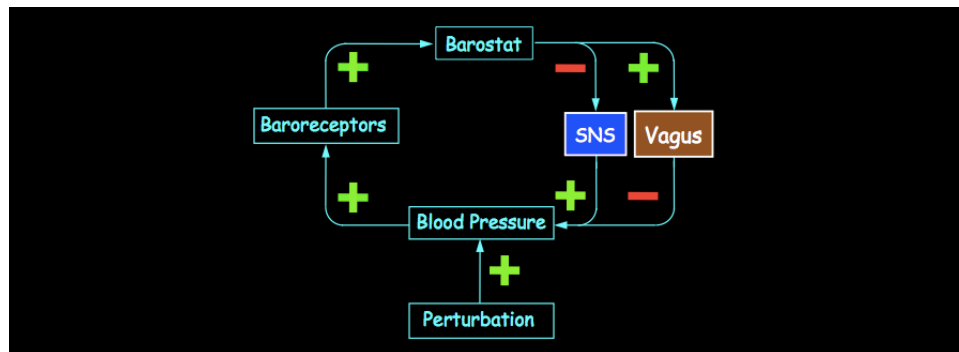


In human's distortion receptors, baroreceptors, in the carotid sinus send afferent traffic to the brainstem.

This is because specialized distortion receptors called baroreceptors lie in the carotid sinus, in the crotch of the “Y” where the common carotid arteries, the main arteries delivering blood to the head, fork in the upper neck. When the blood pressure increases, the wall of the carotid sinus on each side of the neck expands, and this stimulates the baroreceptors in the artery walls. Nerve traffic to the brain then increases in the carotid sinus nerves and reaches a particular cluster of cells in the lower brainstem—the nucleus of the solitary tract, or NTS.

Activation of the NTS cells leads to a rapid, reflexive fall in pulse rate, relaxation of blood vessels, and a less forceful heartbeat. The blood pressure and consequently the blood flow to the brainstem decreases, and the victim loses consciousness.

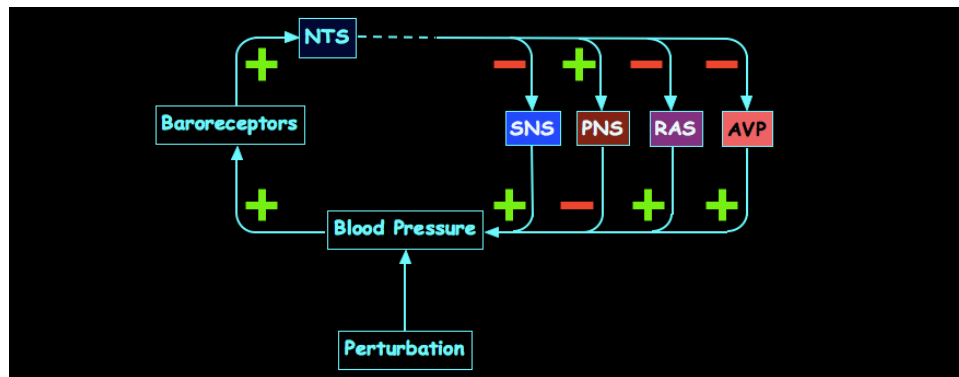
The story of the sleeper hold teaches that one of the most important examples of negative feedback regulation mediated by the autonomic nervous system is the arterial baroreflex.



Arterial baroreceptor activation produces opposite effects on sympathetic noradrenergic system and vagal outflows.

In the arterial baroreflex (from the Greek word for “weight” and the Latin word for “bending back”), when blood pressure increases, distortion receptors fire in the walls of arteries such as in the carotid sinus. Stimulation of the carotid sinus baroreceptors reflexively decreases sympathetic noradrenergic system (SNS) activity, tending to relax the blood vessels and to decrease the force of heart contraction. At about the same time, parasympathetic nervous system (PNS) outflow to the heart via the vagus nerve increases, also tending to decrease the rate and force of heart contraction. The net effect is to bring the blood pressure down.

When blood pressure falls, the SNS is released from baroreceptor restraint, and the increased SNS outflows constrict the blood vessels and increase the rate and force of heart contraction. A sustained decrease in blood pressure also releases the arginine vasopressin (AVP) and renin-angiotensin-aldosterone (RAS) effectors from baroreceptor restraint.



Alterations in blood pressure evoke reflexive changes in activities of several effectors.

Patients with arterial baroreflex failure sometimes have hypertension (chronic high blood pressure) or orthostatic hypotension (a fall in blood pressure when standing), but they always have labile blood pressure.

A key sign of arterial baroreflex failure is blood pressure lability.

Negative Feedback Systems

The stability of the inner world of the body is maintained by negative feedback systems.

Negative feedback regulation is a key—if not the key—mechanism for maintaining physiological homeostasis and is a founding principle of integrative physiology and autonomic medicine. Perhaps surprisingly, Cannon did not formally include negative feedback regulation in his theory.

Negative feedback regulation is a founding principle of autonomic medicine.

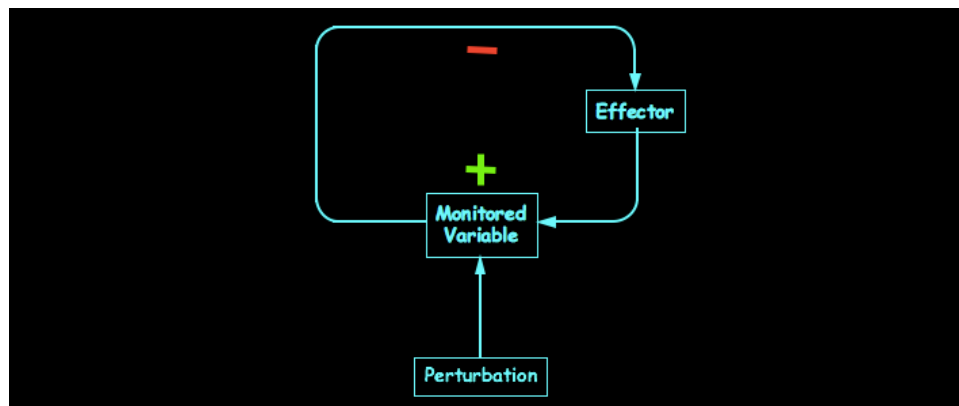
Probably the first researcher to emphasize physiological regulation by negative feedback was the Russian physiologist, Pyotr K. Anokhin (1898-1974) in the mid-1930s. His “theory of functional systems” involved feedback of two types, the first similar to homeostasis for regulation of internal variables such as blood pressure and glucose and the second for regulation of behavioral responses based on feedback from environmental signals.

In a retrospective about Anokhin’s theory, his disciple K.V. Sudakov wrote, “Any deviation of the parameter from the level required for normal life of the organism immediately elicits (through feedback mechanisms or reverse afferentation after Anokhin), a sequence of processes that develop in central and peripheral tissues in order to restore the optimal level of the

given result.” One appreciates readily the equivalence of “reverse afferentation” and negative feedback.

In a physiological negative feedback loop, when a perturbation alters levels of a monitored variable, the activity of an effector changes in a way that counters the effects of the perturbation.

A negative feedback loop has one (or an odd number) of negative relationships in the cycle. When a variable is regulated by a negative feedback loop, in response to a constant perturbation the level of the regulated variable reaches a steady-state value—homeostasis.



A negative feedback loop

Examples of negative feedback regulation mediated by alterations in autonomic outflows abound in autonomic neuroscience. For instance, insulin-induced hypoglycemia, via a complex array of peripheral and central mechanisms, evokes marked sympathetic adrenergic system (SAS) activation and adrenomedullary secretion of epinephrine (EPI), which releases glucose into the bloodstream. Performance of the Valsalva maneuver, which decreases venous return to the heart and

consequently decreases cardiac stroke volume, reflexively increases directly recorded skeletal muscle SNS traffic and total peripheral vascular resistance, attenuating the fall in blood pressure. Standing up (orthostasis) decreases venous return to the heart, and the plasma NE level rapidly increases, indicating SNS activation. Intravenous injection of cold saline evokes increases in both SNS and SAS and outflows, resulting in cutaneous vasoconstriction and calorigenesis and thereby blunts the fall in core temperature.

Simply Standing Up

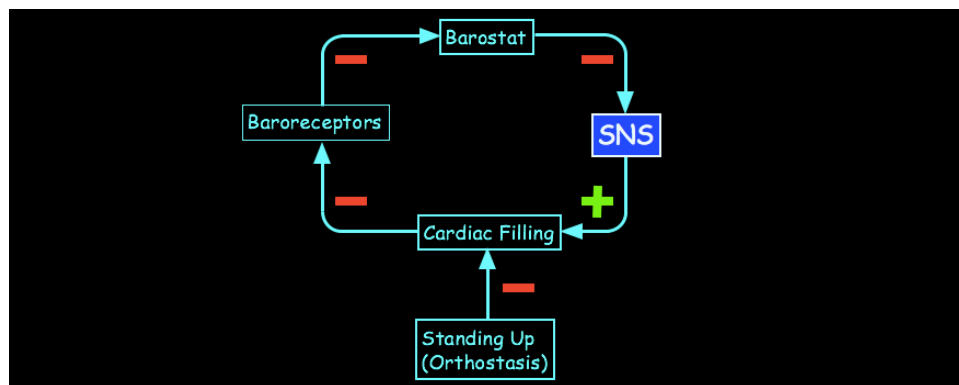
Baroreflexes help maintain the blood pressure.

When a person stands up, the force of gravity tends to pool blood in the legs, lower abdomen, and pelvis. This decreases the return of blood to the heart in the veins. The heart pumps out less blood.

When the heart ejects less blood, information changes in nerves traveling from the baroreceptors to the brain. The brain responds by directing an increase in the activity of the sympathetic noradrenergic system. The sympathetic nerves release norepinephrine, and the norepinephrine activates receptors on cells in the blood vessel walls. This tightens the blood vessels, and so the total resistance to blood flow in the body increases. In other words, the total peripheral resistance increases. Even though the total amount of blood ejected by the heart per minute (cardiac output) has decreased, the average blood pressure normally is maintained, due to the increase in

total peripheral resistance.

You might understand the baroreflex better by thinking about the water pressure in a garden hose. The pressure is determined by how much the faucet is turned on and how much the nozzle is tightened. If you turned down the faucet, the pressure in the hose would decrease, and less water would come out the nozzle. If you wanted to keep the pressure in the hose the same, you could tighten the nozzle. In sympathetic noradrenergic system failure, the patient can't tighten the vascular nozzle.



Baroreflexes involve negative feedback loops (an odd number of “–” signs. This is a simple baroreflex diagram.

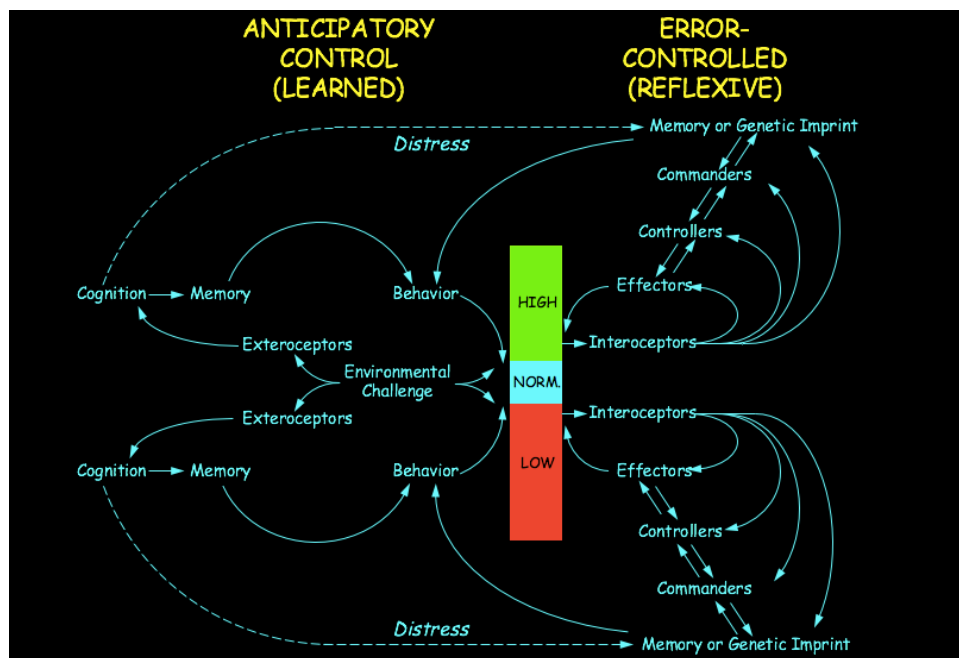
Failure of the sympathetic noradrenergic system always causes orthostatic hypotension.

Reacting to Something That Hasn't Happened

Regulation by negative feedback is essentially reactive. Feed-forward regulation is mediated by anticipatory adjustments in physiological systems based on awareness of a previously experienced or instinctively recognized signal, preceding any

change in the level of the regulated variable itself.

Feed-forward regulation is more efficient than negative feedback regulation, because it diminishes or eliminates the need for homeostatic adjustments. An example is the vagal mediation of the “cephalic phase” of insulin release prior to eating, in anticipation of an increase in blood glucose. Another is the sympathetically mediated hemodynamic changes following “central command” in anticipation of exercise.



Concept diagram showing mechanisms of anticipatory and error-controlled regulation. Under ordinary circumstances, levels of the monitored variable are kept within bounds by anticipatory (learned) control. When this gives way, error-controlled (reflexive) regulation comes into play. Being reactive, error-controlled regulation is associated with increased variability of the monitored variable.

Cannon was referring to feed-forward mechanisms when he noted that internal changes during emotional turmoil prepare the organism for extreme muscular exertion.

The Figure above depicts in some detail regulation by anticipatory control, which usually is learned and mediated by behavior, and by error control, which is reflexive and mediated by effectors such as components of the autonomic nervous system. Under normal circumstances, in response to anticipation of environmental challenges (e.g., going out into the cold outdoors) levels of regulated variables are kept within bounds mainly by anticipatory behaviors (e.g., donning a jacket), the elicitation of which depend on input from exteroceptors (e.g., visual input), perception of the meaning of the input (awareness, e.g., snow is falling), and memory (when snow falls, the weather is cold). The behavior prevents exposure to the environmental challenge from actually altering levels of the regulated variable, in this case core temperature.

When anticipatory, learned behaviors are insufficient, and an actual change in the level of core temperature occurs, this evokes reflexive increases in sympathetic noradrenergic and adrenergic outflows, which by cutaneous vasoconstriction and calorigenesis maintain core temperature. The reflexive responses may include certain externally observable behaviors, such as shivering, piloerection, and folding of the arms. In distress, awareness and memory result not only in behaviors (e.g., flight) but also in changes in reflexive regulation (dashed lines).

Buffering

Buffering is a means of diminishing the intensity of an external disturbance, thereby reducing the required use of reflexive homeostatic mechanisms. Just as insulation in the walls of a house diminishes the requirement of internal adjustment by a furnace in cold weather, many mammals have fur, which creates a layer of motionless air as an insulator above the skin. Other examples of genetically determined insulation based on natural selection in evolution include blubber in whales and closely packed feathers in birds. The barrier to heat loss can be enhanced during more severe cold exposure by reflexive bristling of the hair, mediated by sympathetic nerves; this increases the depth of the layer of motionless air.

In addition to these inherited and acquired forms of buffering, countercurrent heat exchange is a relatively common, efficient mechanism present in animals that limits heat loss through the surfaces of the body exposed to an extremely cold environment (polar regions or ice cold water). The preservation of heat is the result of differences in the temperature in closely adjacent arterial and venous blood vessels. Heat from arterial blood warms the cold venous blood returning from the cold surface, diminishing heat loss from the surfaces exposed to the cold. This arrangement occurs in the feet of penguins standing on ice or birds wading in cold water, the paws of the arctic fox, and the tongue of the whale filtering algae from cold water. The heat transfer between the countercurrent flows depends on the difference in the temperatures and does not require energy other than that required to maintain the flows.

A somewhat more complex countercurrent system in some

species has evolved that cools the brain during exposure to high environmental temperatures. This involves two sequential heat transfers. During inhalation, particularly during panting, moisture evaporation cools the nasal mucosa. A second heat transfer occurs when the cooler venous blood from the nasal mucosa flows into the pterygoid plexus surrounding the carotid rete in a sinus at the base of the brain. Here there is a countercurrent transfer of heat from the warm arterial blood, which flows in the direction opposite to the cooler mucosal venous blood. The cooled arterial blood enters the circle of Willis and is delivered to the brain during exposure to a hot environment. This countercurrent exchange mechanism has been described in detail in sheep and cats and has been reported in a number of other species.

Although humans do not have a carotid rete, it has been hypothesized that the diversity in human craniofacial features (e.g., nostril width) in different geographical regions reflects survival advantages of mechanisms for selective brain cooling in hot environments. Moreover, tonic alterations in sympathetically mediated vasoconstrictor tone may contribute to selective brain cooling

HOMEOSTATS

Students learning about regulation of homeostasis of internal variables are often taught by analogy with a thermostat that regulates the interior temperature of a house. A thermostat is a device that compares the temperature that is set with the temperature that is sensed. When the discrepancy is sufficiently large, the thermostat directs changes in activities of the effector,

such as a furnace, reducing the discrepancy. The level of the monitored variable, in this case the inside temperature, eventually reaches a stable value. The plateau level may not necessarily be the temperature actually set, because this would depend on factors such as the power of the furnace and efficiency of the insulation. Eventually, the inside temperature is held between what is sensed and what is set.

For a given perturbation, the more rapid, sensitive, and powerful the control by negative feedback, the smaller the fluctuations in levels of the monitored variable. When a system regulated by negative feedback is exposed to a fluctuating outside influence, the swings in the levels of the monitored variable are smaller than in the absence of negative feedback.

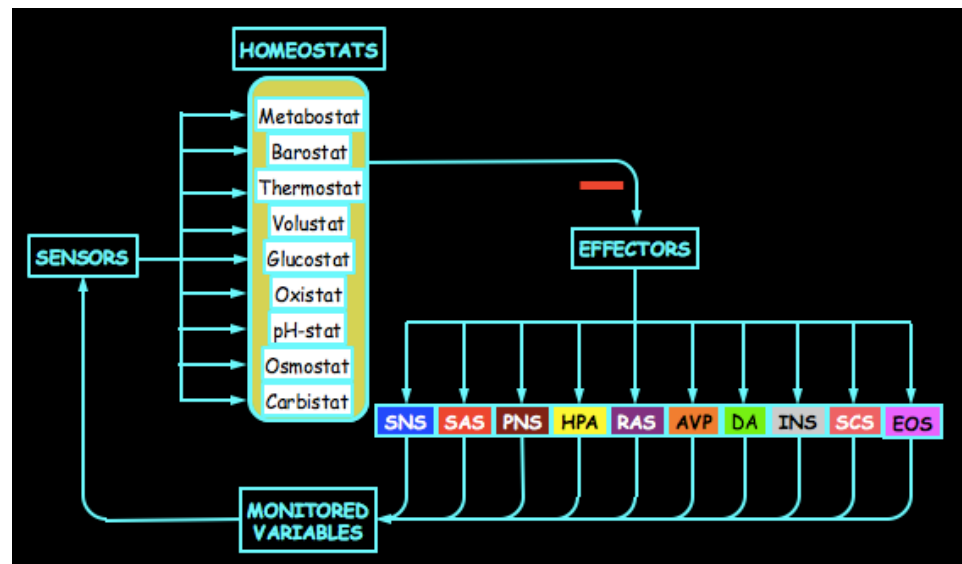
<u>Homeostat</u>	<u>Effectors</u>					
Volustat	SNS	RAS	SAS	AVP	EOS	ANP
Glucostat	INS	SAS	GLU	HPA	GH	PNS
Osmostat	AVP	RAS				
Thermostat	SNS	SCS	SAS			
Na-stat	RAS	SNS	DDA	ANP		
Oxistat	SNS	SAS	EOS			
Barostat	SNS	SAS	AVP	RAS	PNS	NO
Psychostat	SAS	HPA	EOS	PRO	GON	
Metabostat	THY	SAS	SNS			
Nocistat	EOS	SAS	PNS	BRK		
Immune-stat	HPA	CTK				

One can conceptualize the existence of many “homeostats,” each with multiple effectors that result in particular neuroendocrine patterns.

Combined heating and cooling systems, each controlled by a single thermostat that can turn on either the furnace or the air conditioner, constitute a thermostatic system.

One can think of a multiplicity of internal homeostatic systems, each with its own “homeostat” — a “barostat” for regulating blood pressure, a “thermostat” for regulating core temperature, a “glucostat” for regulating blood glucose levels, an “osmostat” for regulating serum osmolality, and so forth.

Homeostats are metaphorical comparators that work like thermostats.



In this schema many homeostats use many effectors to keep levels of many monitored variables within bounds via negative feedback loops.

A key disadvantage of the homeostat idea is that no evidence has accrued for the existence of physiological homeostatic

comparators. One cannot prove that something doesn't exist, but at this point it seems best to view homeostats as metaphors, or models for how the regulation happens—i.e., the body maintains homeostasis *as if* there were homeostatic comparators.

Ashby's "Homeostat"

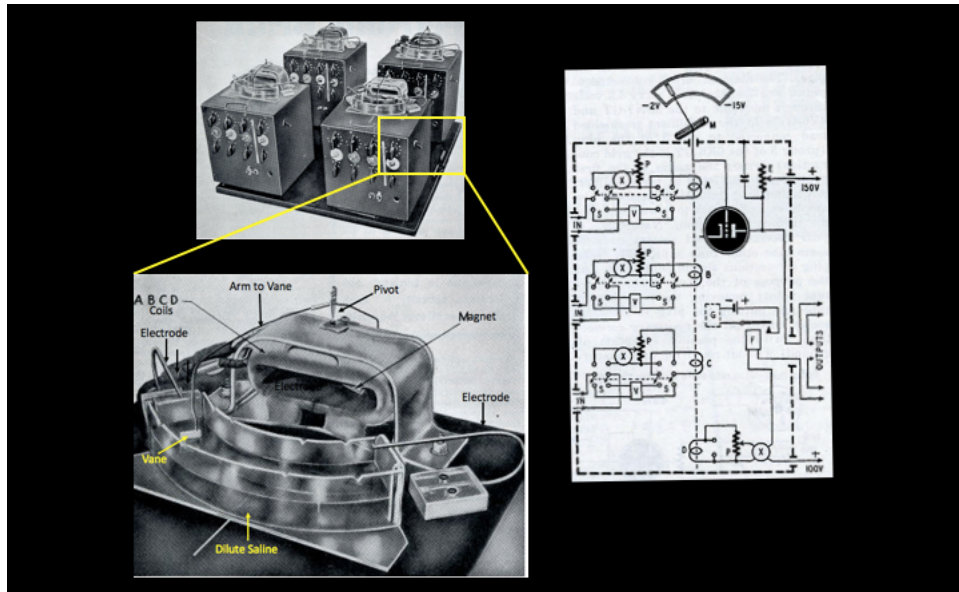
W. Ross Ashby, one of the founders of the fields of cybernetics and complex systems, introduced a machine he called "the homeostat" in the 1940s.

The homeostat consisted of four identical units connected to each other via electrical inputs and outputs. Atop each unit was a semi-circular trough that contained dilute saline solution, with a gradient of potential that conducted a current. An electrically conducting vane was positioned in each trough, and an electromagnet determined the position of the vane.

Displacement of the vane would allow electric current to flow in a manner proportionate to the angle of displacement; this in turn regulated the output from the unit to the other three units and resulted in displacement of their vanes, which created outflows that were fed back to the first unit. When an initial stable setting was disturbed, this machine was able to select from among a variety of nearly 400,000 randomly presented settings and to self-regulate to reach a new stable state.

The multiple possibilities for attaining a stable state led Ashby to describe the homeostat as "ultrastable." In terms of physiology and behavior, an ultrastable system has the capacity to adapt by trial and error learning. The homeostat was one of

the first devices shown to be capable of adapting itself to the environment and stabilizing the system in the face of introduced disturbances. In 1949, an article in *Time* magazine claimed that the homeostat was “the closest thing to a synthetic brain so far designed by man.”



The “homeostat,” built by W. Ross Ashby

In essence, Ashby’s homeostat was a type of electromagnetic machine. No energy was required to keep the needle at its starting point, whereas homeostatic in biology requires energy. Ashby’s homeostat was rather far removed from the concept of the homeostat as in essence a metaphor, but his homeostat deserves mention for historical reasons—and so that you aren’t confused by the use of the same word in the past.

The Birth of Biocybernetics

During a stay in Walter B. Cannon’s laboratory, the Mexican

physician Arturo Rosenblueth became acquainted with Norbert Wiener and Julian Bigelow, who at the time (wartime in the early 1940s) were working on a servo-mechanism-based rangefinder for anti-aircraft guns. Their machine was “intelligent,” in that it could predict the trajectory of an airplane based on the previous trajectories (“memory”); however, when they tried to correct the machine for friction, it developed uncontrollable swings in motion.

Wiener asked Rosenblueth, who had become a neurologist, if there were neurological disorders manifesting similar signs. Rosenblueth described the difficulty of patients with cerebellar injury in drinking a glass of water, due to uncontrolled, oscillatory amplification of voluntary movements. From the similarity of the neurological disorder to malfunction of the rangefinder they realized that both required “a closed loop (negative feedback) allowing the evaluation of the effects of one’s actions and adaptation of future conduct based on past performance.”



Arturo Rosenblueth, Norbert Wiener, and Julian Bigelow developed a theory of control systems that would be applicable to biology – “biocybernetics.”

The authors conceived of the idea that control systems in machines could be designed to emulate the nervous system by negative feedback and to self-regulate using the results of earlier activity to improve the likelihood of attaining the goal. Conversely, close examination of the requirements for ideal control might provide directions in research about how the nervous system is designed to gain control of physiological variables via negative feedback and memory.

Rosenblueth, Wiener, and Bigelow classified behavior in terms of (1) active or non-active, then if active (2) purposeful or non-purposeful, then if purposeful (3) feedback-regulated (teleological) or non-feedback-regulated, and then if feedback-regulated (4) predictive (extrapolative) or non-predictive.

Teleology was not taken to imply “final causes” and was viewed as synonymous with purpose controlled by feedback. Finally—and provocatively—they argued that the “broad classes of behavior are the same in machines as in living organisms,” regardless of the complexity of the behavior.

Rosenblueth, Wiener, and Bigelow first presented their ideas in 1942 to mathematicians, physiologists and engineers attending a seminar at Princeton’s Institute for Advanced Study. The seminar was extremely successful and induced the Josiah Macy Foundation to sponsor a series of such interdisciplinary meetings.

In 1948, Wiener’s book appeared in which he coined the term “cybernetics.” This captured the ideas examined so well that the seminars became known as the Macy Cybernetics Conferences. The participants were attempting to develop a theory of control

systems that would be applicable to a wide variety of disciplines, including biology —“biocybernetics.”

Wiener distinguished two forms of biocybernetics, medical biocybernetics and neurocybernetics. In medical biocybernetics, “homeostasis is the main consideration,” whereas neurocybernetics mainly involves “the pathways of actions via sense-organs, neurons and effectors,” although it was pointed out that “there is no sharp distinction between the two fields.”

The biocybernetic approach to understanding brain functions aroused considerable debate. One of the attendees at the Macy Conferences, John von Neumann, gave this opinion, “The difficulties are almost too obvious to mention: They reside in the exceptional complexity of the human nervous system, and indeed of any nervous system...Nothing that we may know or learn about the functioning of the organism can give, without ‘microscopic’ cytological work, any clues regarding the further details of the neural mechanism.”

Although one may question whether biocybernetics will lead to new discoveries about how homeostasis is maintained by the brain, current experimental therapeutic approaches for disorders of homeostasis can be viewed as applications of biocybernetics. Carotid sinus stimulation or renal sympathetic radiofrequency ablation may attenuate refractory hypertension. Intravenous infusion of norepinephrine or an automated abdominal binder may mitigate neurogenic orthostatic hypotension; and vagus nerve stimulation, by directly or reflexively evoking effects on elaboration of cytokines, may be useful to treat conditions involving auto-immunity such as rheumatoid arthritis.

Ashby's Law of Requisite Variety

Ashby's law of requisite variety states that for a system to be stable, the number of states of its control mechanism must be greater than or equal to the number of states in the system being controlled. Ashby's homeostat included requisite variety, because the pattern of feedback within the homeostat depended on the value for a uniselector changing every 2-3 seconds among 390,625 possible combinations.

According to Ashby, the occurrence of good regulation in control of the internal environment by the brain is the product of eons during which natural selection has acted on requisite variety of control systems.

Norbert Wiener, in his classic book, *Cybernetics: or Control and Communication in the Animal and the Machine*, agreed when he wrote, "...among the varied patterns of behavior which are propagated some will be found advantageous...and will establish themselves, while others that are detrimental...will be eliminated. The result is a certain sort of racial or phylogenetic learning...Both phylogenetic learning and ontogenetic learning are modes by which the animal can adjust itself to its environment."

Examples of requisite variety include the genetic variety required to favor alternative genotypes in evolution; "canalization" in embryology, such that despite variations in developmental reactions the same end results are reached; and behavioral variety required for shaping in operant conditioning.

To paraphrase Ashby, variety is necessary to destroy variety. It is variety that enables stability.

Good Regulators

Ashby's Good Regulator theorem (proven mathematically by Conant and Ashby) states that a good regulator models well the system it regulates—like a good key models its lock.

The word, “good,” means that the regulator is maximally efficient and simple: each value of the regulator corresponds to one and only one value of the regulated variable.

Conant and Ashby wrote, “The theorem has the interesting corollary that the living brain, so far as it is to be successful and efficient as a regulator for survival, must proceed, in learning, by the formation of a model (or models) of its environment.” In order to achieve stability, autonomous systems must have in place an internal model of their environment; however, having such a model of itself is insufficient and requires negative feedback effects on the regulator. In other words, requisite variety enables the human brain to function as an assemblage of good regulators acting in parallel, providing close correspondences between myriad models and reality; however, good regulation does not imply that the regulated variable is kept within bounds—homeostasis.

Conant and Ashby also described the difference between what they called “error-controlled” and “cause-controlled” regulation. A simple thermostatic system is error-controlled, in

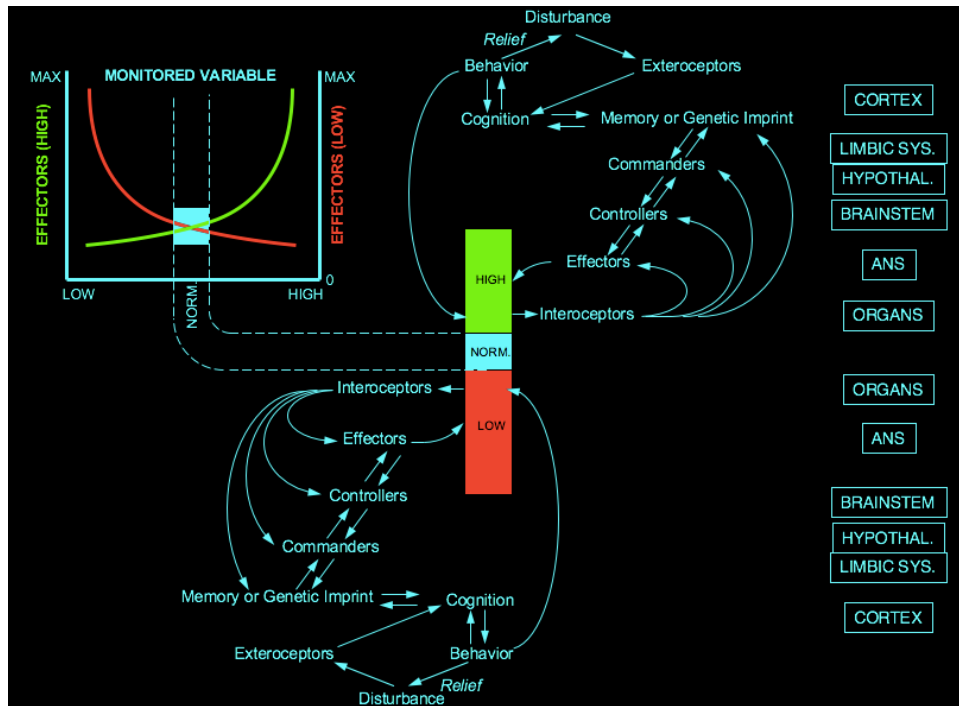
that first the temperature must change before the furnace can turn on; however, as they wrote, “The error-controlled reflex acts, in fact, only as reserve: ordinarily, the nervous system senses, at the skin, that the cause of a fall has occurred, and reads to regulate before the error actually occurs. Error-controlled regulation is in fact a primitive and demonstrably inferior method of regulation. It is inferior because with it the entropy of the outcomes...cannot be reduced to zero: its success can only be partial. The regulations used by the higher organisms evolve progressively to types more effective in using information about the causes...as the source and determiner of their regulatory actions.” The notions of error-controlled and cause controlled regulation fit squarely with negative feedback and anticipatory (feed-forward) regulation.

Homeostasis without Homeostats

For each monitored variable there seems to be a hierarchy of negative feedback loops, from cells to organs to brainstem reflexes to hypothalamic primitive behaviors to higher centers mediating conscious, voluntary behaviors.

The concept diagram below presents an overview of pathways and relationships by which central neural processes regulate levels of monitored variables via the autonomic nervous system. The levels are kept within bounds because of changes in effectors when the levels increase (green) and complementary changes in other effectors when the levels decrease (red).

The effector responses are determined not only by sensory input



Homeostasis of a monitored variable by two complementary effectors, green responding to increases and red to decreases. Changes in the level of the monitored variable beyond a limit evokes effects at multiple levels of the neuraxis, and the level of the monitored variable is kept within bounds without a comparator (i.e., a homeostat). There are multiple input-output relationships at ascending strata in the neuraxis, from the target organ to lower brainstem “controller” sites mediating reflexes, to upper brainstem/hypothalamic “commander” sites mediating patterned instinctive responses, to limbic sites involving emotional memory and classically conditioned learning, to cortical sites involving social consciousness, restraint of lower centers, instrumentally conditioned learning, and interactions with the environment.

by the target cells (e.g., glucose sensing by pancreatic islet cells) but also by spinal and brainstem reflexes, based on input

from interoceptors, as if there were “controllers.”

The brainstem reflexes in turn are modulated by instinctive behaviors generated by activation or inhibition of hypothalamic centers, also dependent on sensory input, as if there were “commanders.” The hypothalamic instinctive patterns are modulated by classically conditioned emotional feelings based on input from limbic centers and depending on habituation, sensitization, and imprinting.

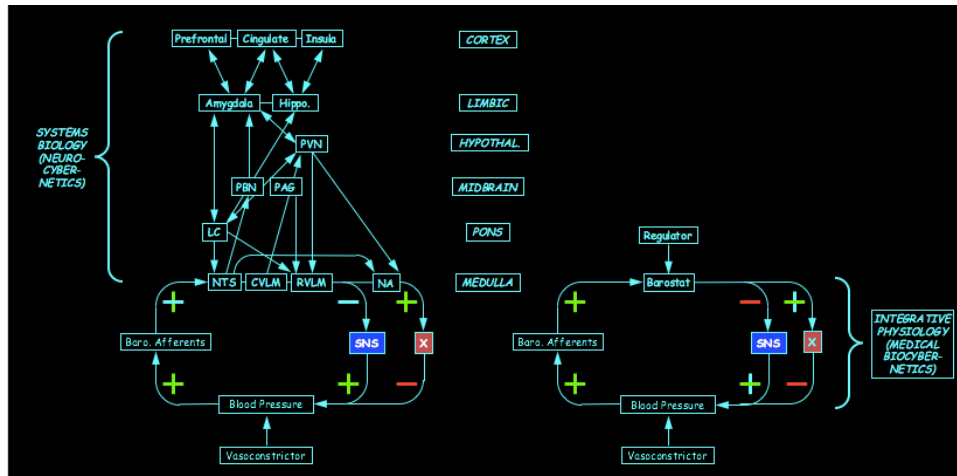
Cortical centers are responsible for cognitions, instrumentally (operantly) conditioned learned behaviors, simulations of future events, and largely restraining social psychological instructions, based importantly on interpretations of environmental stimuli.

Although it may be tempting to postulate that there are multiple internal homeostatic systems, each with its own “homeostat”—a “barostat” for regulating blood pressure, a “thermostat” for regulating core temperature, a “glucostat” for regulating blood glucose levels, an “osmostat” for regulating serum osmolality, and so forth—no comparator has been identified for any regulated internal variable.

Homeostats are metaphors or models for how the regulation happens—i.e., the body maintains homeostasis *as if* there were homeostatic comparators. Our concept is of complementary, complex interactions of neuronal networks that function as “stats,” orchestrating a variety of behavioral and physiological responses.

I think Ashby’s Good Regulator theorem gives meaning to the homeostat as a metaphor, and his law of requisite variety

explains how brain networks maintaining homeostasis evolved



The “barostat” as a metaphor. (Left) Input-output curves in the central autonomic network. (Right) Adjustments in input-output curves give the appearance of resetting a hypothetical barostat.

and are modified by experience.

Stress

SELYE'S "STRESS"

Cannon rarely referred to stress; when he did so he always meant an imposed threat to homeostasis.

Hans Selye popularized stress as a scientific idea.

In a famous letter to *Nature* in 1936 Selye described for the first time what he came to refer to as the “syndrome of just being sick.” He injected an extract of ovary tissue in rats for several

months and found that the treatment resulted in stomach ulcers, enlargement of the adrenal glands, and shrinkage of the lymph nodes and thymus. To his surprise, control rats that received injections of inactive placebo developed the same pathologic triad. Both the experimental and control rats often avoided injection attempts or wriggled free and had to be chased around the laboratory with a broom.

Selye proposed that both the experimental and control animals underwent “stress,” which he defined as the non-specific response of the body to any demand imposed upon it.

Selye’s theorized that a General Adaptation Syndrome occurs in three stages. The first stage, the “alarm reaction,” corresponds to Cannon’s “fight or flight” reaction and includes release of what Selye referred to as “adrenalines” from the adrenal gland. The second stage is adaptation, and the third is exhaustion.



Hans Selye (1907-1982), father of “the stress response”

According to Selye, all challenges to homeostasis are met by both specific and non-specific responses. It is the shared element, the non-specific response, that is stress.

Initially Selye used the term “stress” in the same sense as did Cannon. Ambiguity about whether stress is a disturbance that threatens homeostasis, a state produced by the disturbance, or a non-specific response to the state, led to the critical observation, “...stress, in addition to being itself and the result of itself, is also the cause of itself.” Subsequently, Selye defined a new word, “stressor,” as that which results in a state of stress.

The ambiguity did not disappear, however. In the remainder of this book, “stressor” is used to denote a disturbance, “stress” a state resulting from the effects of the disturbance, and stress response altered activity of one or more effectors as a result of stress.

Subsequently it was shown mathematically that without simplifying assumptions Selye’s doctrine of non-specificity cannot be disproved, meaning that it has limited scientific value.

The doctrine of non-specificity was shown to be testable, given certain assumptions. It predicted equal ratios of responses of plasma corticotropin and epinephrine levels between low- and high-intensity stressors, regardless of the stressor; however, this was shown clearly not to be the case for all stressors. Given the simplifying assumptions that rendered the doctrine of non-specificity testable, the experimental data were inconsistent with Selye’s stress theory and refuted the existence of a unitary stress syndrome.

Current concepts view stress responses as having a degree of “primitive specificity,” depending on the particular challenge and on the organism’s perceived ability to cope with the stressor. Components of the autonomic nervous system play important roles in all of them.

According to this idea, each stressor has a neurochemical “signature,” with quantitatively if not qualitatively distinct central and peripheral mechanisms. The neurochemical changes do not occur in isolation but are orchestrated along with physiological, behavioral, and experiential changes and depend on the history of exposures to the same or different stressors and the organism’s perceived ability to cope with the stressor.

In evolutionary terms, by enhancing survival, natural selection would have favored such patterning of stress responses. Nevertheless, Selye’s notion of a non-specific “stress syndrome,” mediated by a central “stress system,” persists and remains widely used.

Selye did not view stress as necessarily harmful. Relatively late in his career, he coined the term “eustress,” for stress that is not harmful and possibly even helpful to the body, and “distress,” for damaging or unpleasant stress. Excessive, repeated, or inappropriate stress responses were viewed as maladaptive. Selye proposed an immense list of diseases of adaptation, from adrenal gland tumors to hypertension, vasculitis, diabetes, allergy, and psychosomatic disorders.

Defining distress solely in terms of pathology is inherently

circular and consequently of limited scientific value. We have proposed a non-circular definition, according to which distress is a form of stress that is conscious, aversive, generates instinctively communicated signs, and is associated with adrenocortical and adrenomedullary activation. These aspects are discussed later in this chapter.

HOMEOSTATS AND STRESS

Although the body regulates numerous monitored variables by negative feedback, no one has actually identified any homeostats, in the sense of actual physiological comparators. Homeostats such as the “barostat” regulating blood pressure, the “osmostat” regulating serum osmolality, the “glucostat” regulating serum glucose, the “thermostat” regulating core temperature, and so forth, while useful as concepts of integrative physiology, are metaphors.

A Homeostatic Definition of Stress

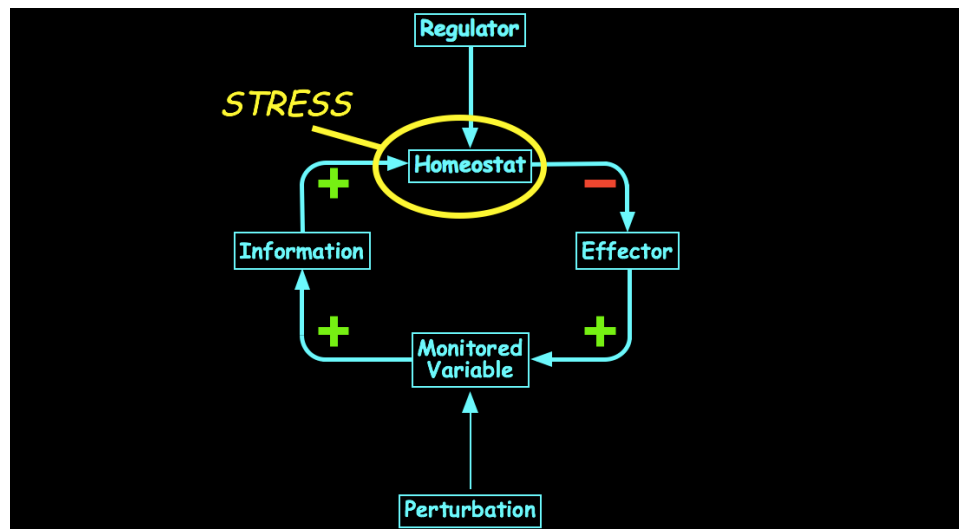
If homeostats are metaphors and are unnecessary for understanding how homeostasis happens, what good are they? For one thing, the notion of homeostatic comparators leads straightforwardly to a definition of stress.

Stress is a condition in which the brain senses a discrepancy between information about the “inner world” and instructions for responding.

According to the homeostat theory, stress is neither stimulus

nor a stereotyped response pattern but is a condition, a state in which there is a perceived discrepancy between information about the level of a monitored variable and an algorithm for responding, and the discrepancy leads to alterations in activities of effectors—including components of the autonomic nervous system—that reduce the discrepancy.

In stress, the brain perceives a discrepancy between afferent information and an algorithm for responding, and the error signal drives the response. The response, in turn, alters the state, in a negative feedback loop. Just like a memory, or a motivational state, or an emotional feeling, the algorithm doesn't actually exist anywhere specifically in the brain.



The homeostat idea leads directly to a definition of stress as a condition in which there is a perceived discrepancy between information and a set-point for responding.

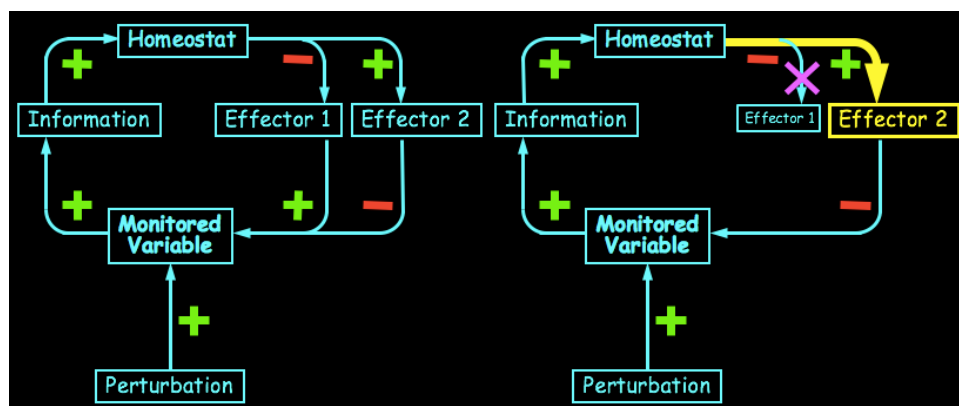
It seems to me that all stress responses are mediated in one way or another by alterations in activities of components of the autonomic nervous system. The responses of the autonomic

effectors are associated with behavioral and experiential components. The autonomic responses are automatic. They are unconscious and involuntary, until the afferent information arises in the central neural hierarchy to above the level of medullary reflexes; they aren't really autonomic at all.

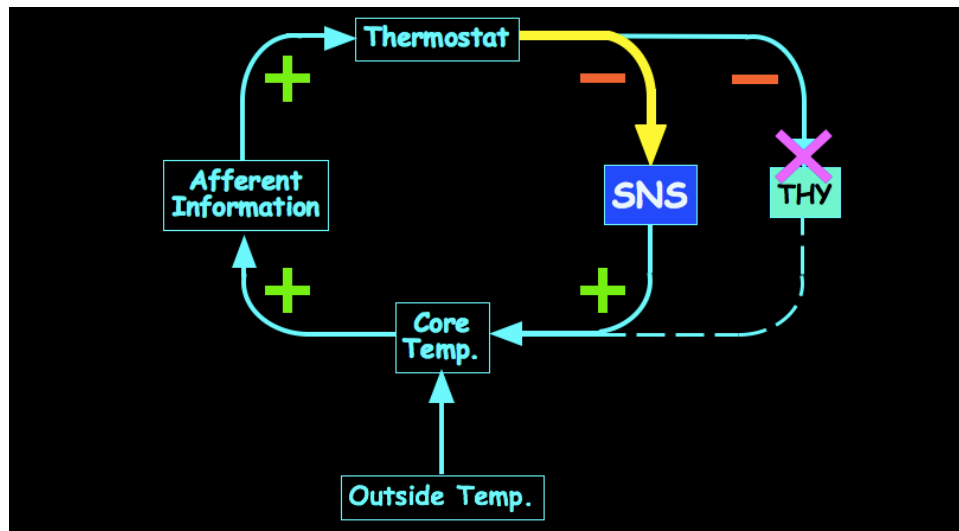
Multiple Effectors and Compensatory Activation

All the key monitored variables of the body are regulated by more than one effector. For instance, blood glucose levels are determined by insulin, glucagon, adrenaline, and cortisol.

Having multiple effectors offers clear survival advantages. First, having multiple effectors allows at least some degree of control of the monitored variable if one effector is disabled. This is called “compensatory activation.” Compensatory activation helps explain why, for instance, patients who are hypothyroid have increased sympathetic noradrenergic system activity.



Having multiple effectors enables compensatory activation. Here, when Effector 1 is disabled, Effector 2 is more active.



Compensatory activation of the sympathetic noradrenergic system (SNS) helps explain why hypothyroid patients have increased SNS activity.

Second, having multiple effectors extends the range of control of the monitored variable. Consider how adding an air conditioner to a furnace extends the range of control of the temperature inside your house.

Third, having multiple effectors permits the evolution or learning of relatively specific patterns of response that are most adaptive for particular stressors. This is in line with Ashby's law of requisite variety.

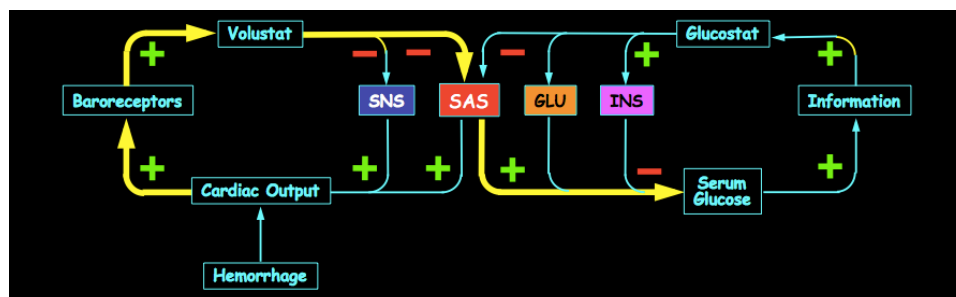
Multiple Homeostats and Effector Sharing

The homeostatic systems of the body can share effectors.

For instance, a patient who has low blood pressure due to gastrointestinal hemorrhage can have elevated serum glucose

levels, because both the “volustat” and “glucostat” use the sympathetic adrenergic system (SAS) as an effector. One may reasonably propose that all medical or surgical emergencies tend to raise glucose levels, because of sharing of the SAS effector. I would guess that “normal” blood glucose levels are high in samples coming from the emergency room.

Analogously, patients with congestive heart failure often have a low serum sodium concentration. Via release from baroreceptor restraint, heart failure stimulates the sympathetic noradrenergic system, the vasopressin system, and the renin-angiotensin-aldosterone system. Norepinephrine, vasopressin, and angiotensin II help maintain systemic blood pressure; however, vasopressin is also the anti-diuretic hormone used by the “osmostat” to force the kidneys to retain free water, and angiotensin II is a potent stimulant of the experience of thirst. The combined effects of vasopressin and angiotensin II can explain the low serum sodium concentration attending heart failure. In this setting the appropriate treatment would not be infusion of hypertonic saline, nor restriction of water intake, but measures to alleviate the heart failure.



Sharing of the SAS by two homeostats (the volustat and the glucostat) helps explain why cardiovascular shock is associated with high glucose levels.

Stress, Allostasis, and Allostatic Load

According to the concept of homeostasis, the brain coordinates body systems, with the aim of keeping values for key internal variables within bounds. According to the more recent concept of allostasis, the acceptable bounds change with circumstances.

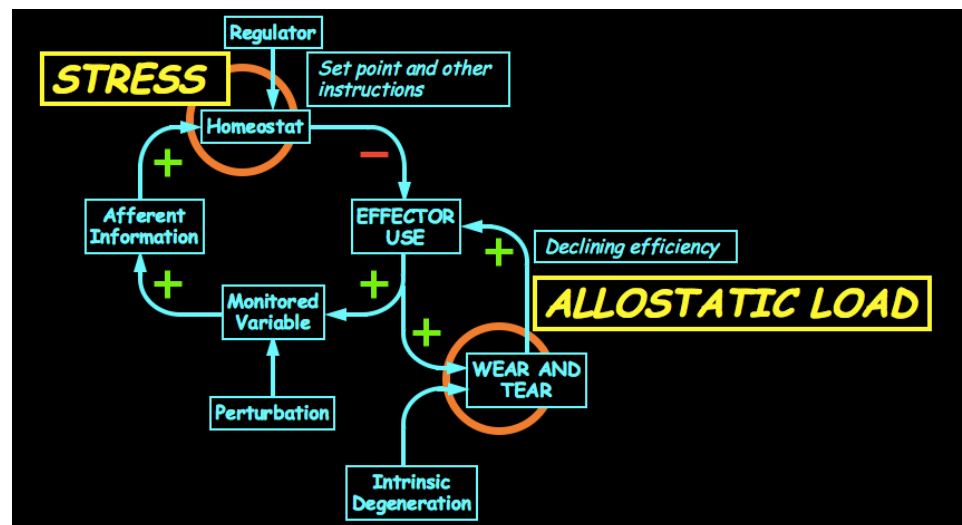
A low-grade fever when you have the flu is an example of allostasis.

Anyone who has had a bad cold with a low-grade fever for a few days knows from personal experience what allostasis is. Your core temperature is higher, your pulse rate is faster, you lose your appetite, you curl up in bed, you sleep more, you withdraw socially, and you become cranky. You are “not yourself.” When you have an acute illness like this, the levels of variables of internal variables do not change in a completely uncontrolled way. Your core temperature is regulated, but the virus somehow resets the thermostat. Once you recover and are back to your “old self,” all the homeostatic settings return to those before the acute illness, with no damage done.

But suppose the low-grade fever and other symptoms and signs don’t resolve so quickly. Maybe they persist or worsen over weeks or months. Then you become enfeebled, bedridden, disabled, disheveled, and disheartened. You undergo blood tests, scans, biopsies, hospitalizations, surgeries, treatments, complications, and rehabilitation. The incomplete recovery reflects effects of allostatic load. To patients with dysautonomias, this scenario probably sounds all too familiar.

Allostatic load refers to effects of prolonged activation of effectors involved in allostasis. Allostatic load is like the wear and tear on your furnace as it cycles on and off during the winter. If you turned the thermostat way up, the furnace would be on more of the time, and there would be more wear and tear on its components.

If you not only turned the thermostat up but also left a large window open for the entire winter, there could be enough wear and tear on the furnace that it would fail completely.



Homeostatic definitions of stress and allostatic load

Let's consider this a bit more. Because of the wear and tear, the efficiency of the furnace declines. When the efficiency declines, then because of the negative feedback loop, the furnace is on more of the time. Because the furnace is on more of the time, there is more wear and tear, and the efficiency declines further. This is an example of a positive feedback loop. The transition from a negative feedback loop to a positive feedback loop is a transition from a stable to an unstable

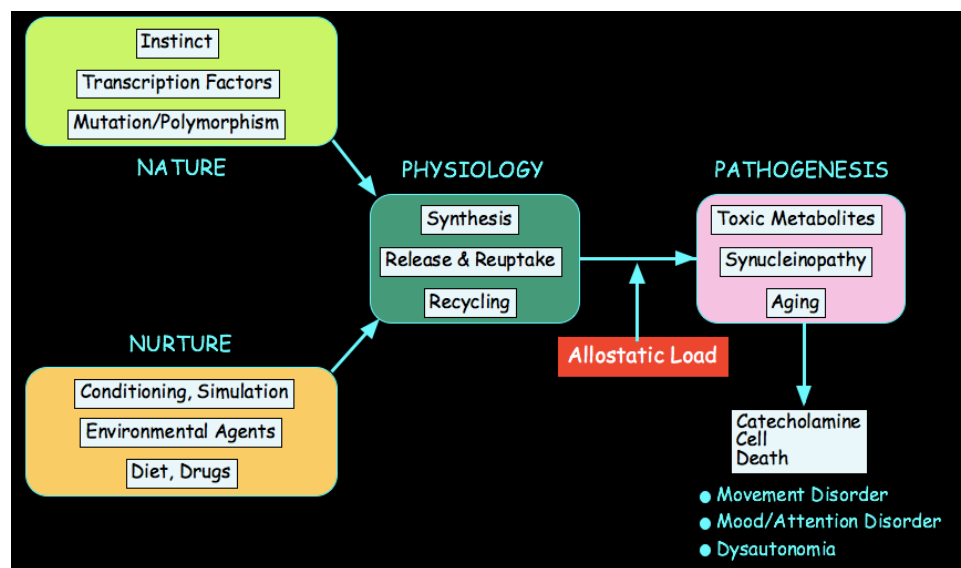
internal environment and the end of homeostasis.

Allostatic load links stress with degenerative diseases.

Activation of effectors to counter threats to homeostasis produces wear and tear on the organs determining the level of the monitored variable and on the effectors themselves.

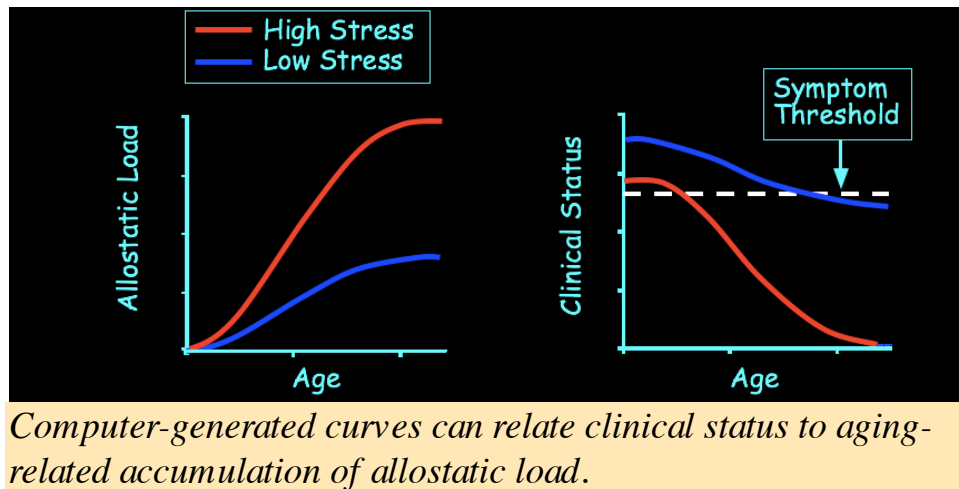
Compensatory activation also can increase allostatic load, due to effects of augmented activity of the alternative effectors.

Allostatic load corresponds to long-term wear and tear.



Where allostatic load fits in the area of diseases involving loss of catecholamine neurons.

Wear and tear, combined with planned obsolescence, decreases effector efficiency. The same perturbation then results in greater wear and tear and further decreases effector efficiency. Eventually, even with the effectors activated continuously, the



monitored variable drifts from the allostatic setting. Finally, when the effectors fail, the organism can no longer mount a stress response at all.

DIFFERENTIAL SNS & SAS RESPONSES TO STRESSORS

Differential plasma epinephrine (EPI, adrenaline) and norepinephrine (NE) responses across different stressors provide strong evidence that, in contrast with Cannon's view, there is no monolithic sympathoadrenal response to all stressors.

The sympathetic adrenergic system (SAS) is very sensitive to decreases in glucose availability, such as from insulin-induced hypoglycemia, and to emotional distress. (Indeed, increased plasma EPI may be the most sensitive index of distress.)

The sympathetic noradrenergic system (SNS) is very sensitive

to cold exposure, isometric or mild exercise, active avoidance or escape behavior, and orthostasis (upright posture).

	SNS	SAS
2-Deoxyglucose (glucoprivic stress)	+	++++
Distress	+	+++
Autonomically mediated syncope (fainting)	+	++++
Orthostasis	++	+
Mild exercise	++	+
Cool temperature at skin of back	+++	0
Mild core hypothermia	+++	+

Adrenaline and norepinephrine responses to some stressors change differentially.

Across stressors plasma EPI responses are more closely tied to responses of the hypothalamic-pituitary-adrenocortical (HPA) axis than to responses of the SNS. One can conceptualize the existence of a unitary adrenal (adrenocortical/adrenomedullary) system just as well as a unitary sympathoadrenal system.

Distress

A non-circular definition is required to enable experimental testing about the health consequences of distress.

A non-circular definition of distress is that it is a form of stress with additional characteristics—consciousness, aversiveness, observable signs, and adrenal gland activation. Each of these aspects receives attention below.

CONSCIOUSNESS

The occurrence of stress does not require consciousness. In contrast, distress does require consciousness, because distress involves not only a challenge to homeostasis but also a perception by the organism that homeostatic mechanisms may not suffice—that is, interpretation of afferent information and simulation of future events. An organism experiences distress when it perceives the inadequacy of compensatory adjustments to either a psychological or physiological stressor.

AVERSIVENESS

Distress is negatively reinforcing and motivates escape and avoidance learning. Distressed organisms avoid situations that are perceived as likely to reproduce the same aversive experience.

The experience of distress enhances vigilance behavior and long-term memory of the distressing event. These are adaptive adjustments that must have offered tremendous survival advantages in evolution. In considering potential long-term health consequences of distress, such as post-traumatic stress disorder, one must bear in mind its important survival advantages.

Most animals can react instinctively not only to a stressor but also to symbolic substitutes that resemble the natural stimulus. The plasticity afforded by learning decreases the likelihood of inappropriate instinctive responses to symbolic cues. Even

primitive animals can learn to withdraw or escape from noxious stimuli or to habituate after prolonged or repeated exposure to a stimulus.

Classical conditioning, or Pavlovian conditioning, represents a refinement of these responses, in that habituation and sensitization are forms of “non-associative” learning, where the organism learns about single stimuli, whereas classical conditioning (and operant conditioning, to be discussed shortly) involves learned associations between stimuli.

Instrumental conditioning, or operant conditioning, represents an even more advanced form of learning that requires a cerebral cortex. The conditioning is “operant” in that the individual’s behavior operates on the environment, determining the occurrence of reinforcement (reward); and the conditioning is “instrumental” in that the learning is a means to an end, since the occurrence of reinforcement depends on the behavior. Operant conditioning differs from Pavlovian or classical conditioning, in which the delivery of the reinforcement occurs independently of the individual’s behavior.

If an organism experienced distress consistently in a given situation, subsequent perception of re-exposure to the situation could elicit distress as a classically conditioned response. Classically conditioned distress could then motivate acquisition of instrumentally conditioned avoidance behaviors. Situations evoking distress typically involve a complex interplay of classical and operant conditioning and arouse coordinated skeletal muscle and autonomic responses.

INSTINCTIVELY COMMUNICATED SIGNS

A third characteristic of distress is the evocation of signs that others can interpret as indicating the emotional state and intent of the organism. Perceptions of signs of distress by other members of the species elicit involuntary, instinctive responses. Even in humans, the fiercest combat usually ends abruptly when one side shows a universally understood sign of surrender and submission.

One such sign is waving a white flag—perhaps because of an instinctive association of pallor with defeat. In English, “wan,” “pallid, and “pale” refer not only to skin turning white but also to weakness or feebleness. In contrast, waving a red flag is taken as an incitement and as an indicator of danger. We turn white with fright but red with rage.



Pallor is a well recognized sign of fright. Note the white hand of the dauphin in Lucien Meunier's 1879 painting, “Le prévôt des marchands Etienne Marcel et le dauphin Charles.”

The communication value of external signs of distress helps to explain the continued elaboration of observable components of distress responses in modern society, despite the relative rarity of true fight-or-flight reactions in humans. During the course of human evolution, these signs originally may have been by-products of genetically determined neurocirculatory adjustments supporting fleeing and fighting. In modern society, they continue to serve important signal functions.

Distress and the OJ Simpson Case

You probably remember the highly publicized OJ Simpson case, in which the football and movie star stood accused of killing his divorced wife, Nicole Simpson Brown, and a friend of hers, Ron Goldman, in a fit of jealous rage on June 12, 1994.

He had a potential alibi. He was on a 11:45 PM red-eye flight to Chicago. If the murder had occurred late enough in the evening, then too little time would have elapsed for Simpson to have committed the crime and then get to the airport. The case hinged on the timing of the murder. The forensic evidence could not pinpoint the timing accurately enough to reject the alibi.

An instinctively communicated sign of distress may have timed the murder accurately. One of the neighbors testified that he had heard a the “plaintive wail” of a dog at around 10 to 15 minutes after 10:00 PM, while he was at home watching the 10 o'clock news. Another neighbor reported loud, persistent barking also at around 10:15 PM, which interfered with her

sleep.

Neighbor Steven Schwab testified that while he was walking his dog in the area near Brown's house at around 11:30 PM, he came across Brown's pet akita dog trailing its leash. The dog had bloody paws but was otherwise uninjured. Schwab stated he brought the dog to another neighbor, who took the dog out for a walk at approximately midnight. The dog tugged on its leash and led him to Brown's house. That was how Nicole Simpson Brown's dead body was found.

You might ask how, months later, people could remember the exact time at which they heard a dog bark. Dogs bark all the time; no one remembers a bark. But this wasn't a bark. This was a wail, a "plaintive wail." Wailing instinctively conveys the misery of grief. It is almost as if the individual is sharing the agony that a loved one suffered while dying. This communication is generated instinctively and understood instinctively, even by members of an entirely different species. It is a sign of distress in both humans and dogs. Throughout evolution, communication of the experience of distress has offered important information relevant to survival. The incident, the circumstances, the timing, and one's sensations, emotions, and actions become etched in memory.

The assault, struggle, and death of its master, which evoked the wail by Nicole Simpson Brown's pet dog, must have occurred beforehand. If so, then there would have been enough time for OJ Simpson to have committed the crime and ride to the airport.

ADRENAL ACTIVATION

A fourth characteristic of distress is adrenal gland activation. This involves enhanced release of catecholamines from the adrenal medulla and of glucocorticoids from the adrenal cortex.

Plasma levels of EPI constitute an extraordinarily rapid and sensitive chemical index of this activation and therefore of experienced distress. The EPI response is so rapid that when an animal is killed by decapitation, arterial EPI levels are increased by about 80-fold, while concurrently obtained glucocorticoid levels are unchanged.

Cannon viewed the neural and hormonal components of the “sympathico-adrenal” system as functioning as a unit to preserve homeostasis in emergencies. A more modern view holds that it is specifically the adrenomedullary hormonal component that characterizes distress, while sympathetic noradrenergic system outflows can increase, decrease, or stay the same, depending partly on whether there is a locomotor response (e.g., escape behavior), which entails increased skeletal muscle sympathetic noradrenergic outflows.

Just as there are relatively specific responses to orthostasis, altered environmental temperature, glucoprivation, salt deprivation, and so forth, there are also relatively specific distress responses. In other words, “fight” is not the same as “flight,” “fright,” “fume,” “fret,” or “defeat.”

Nor “faint,” as you will learn later.

Don't Do This at Home

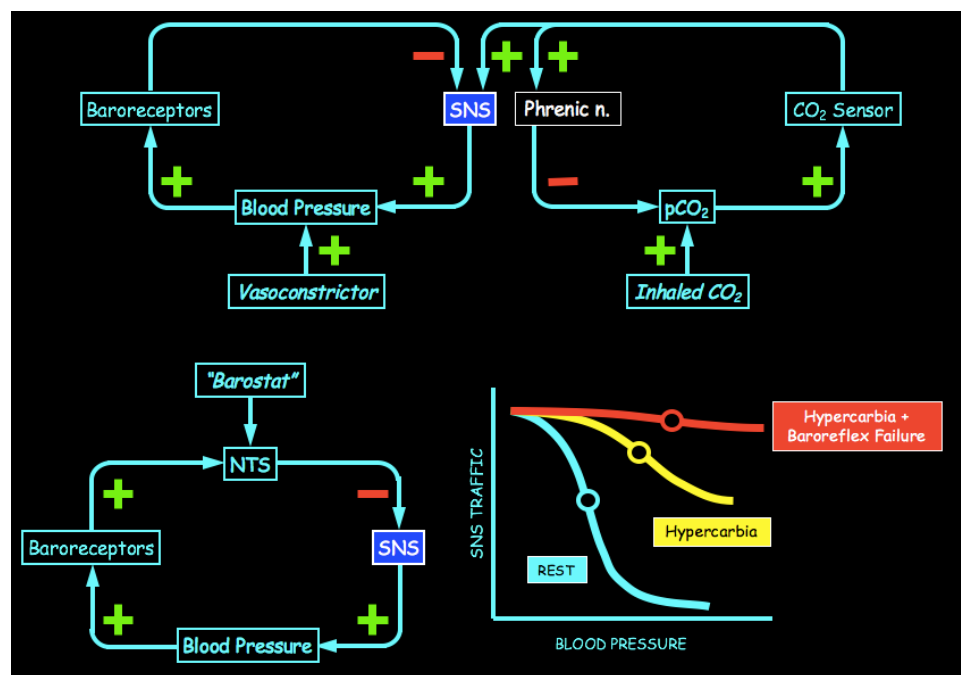
Several years ago I evaluated a patient at the NIH for a difficult form of dysautonomia. The experience taught me a scary lesson about interactions among chemoreflexes, baroreflexes, and distress.

The patient carried a diagnosis of “complex” sleep apnea. For this he had been treated with continuous positive airway pressure (CPAP) using a device he brought with him and used throughout his inpatient stay. The device had been modified to administer a small percent of carbon dioxide with the CPAP, to alleviate episodes of hyperventilation and agitation he had experienced with CPAP alone. Upon autonomic function testing during the day, his directly recorded brachial systolic blood pressure was very high at about 250 mmHg. He had marked baroreflex-cardiovagal failure and very high arterial plasma norepinephrine and adrenaline levels. His discharge diagnosis was extreme sympathetically mediated hypertension.

When you are exposed to a decreased amount of oxygen or to an increased amount of carbon dioxide in the inhaled air (hypoxia or hypercarbia), or when the amount of acidity in your blood increases, your rate and depth of breathing increase. This is an automatic, involuntary, unconscious response. The main effector is the phrenic nerve supplying the diaphragm. One might reasonably argue that such a reflex qualifies as autonomic; however, since the phrenic nerve emanates from the cervical spinal cord and is not post-ganglionic (although it does contain sympathetic post-ganglionic fibers), by Langley's definition reflexive hyperventilation would not be considered to

be autonomic.

On the other hand, hypoxia and high blood carbon dioxide increase activity of the sympathetic noradrenergic system (SNS). This aspect of the chemoreflex surely would be considered autonomic. The extent of SNS stimulation is especially pronounced in the setting of baroreflex failure.



One can model chemoreflex-baroreflex interactions without or with a comparator homeostat.

One can conceptualize two types of negative feedback models predicting changes in the relationship between SNS outflow and blood pressure in the setting of hypercarbia. According to one model, inhalation of carbon dioxide stimulates brainstem chemoreceptors, and the chemoreceptor stimulation both increases ventilation and increases SNS outflows, raising blood pressure. That is, hypercarbia shifts to the right the curve

relating SNS traffic to blood pressure. Baroreceptors restrain SNS outflow, and interference with this restraint (such as by panic/anxiety) augments the SNS and pressor responses to hypercarbia.

According to another model, a metaphorical “barostat” regulates how neurons in the nucleus of the solitary tract (NTS) respond for a given amount of baroreceptor afferent traffic. Hypercarbia alters the set-point for responding, so that blood pressure is regulated at a new level (allostasis). Anxiety decreases baroreflex-sympathoneural gain, enhancing the stimulatory effects of the hypercarbia and SNS outflows and blood pressure.

A reasonable pathophysiologic explanation for the patient’s severe, sympathetically-mediated hypertension syndrome would be a positive feedback loop involving baroreflex failure due to panic/anxiety and repeated episodes of chemoreflex stimulation due to carbon dioxide self-administration.

“EUSTRESS” REVISITED: ADAPTATION AND RESILIENCE

Higher organisms have capabilities to habituate, anticipate, heal, regenerate, and in general increase resilience. These processes may operate at multiple sites within homeostatic loops to increase the useful life of the effectors for the same amount of chronic exposure to a stressor.

Defining distress and “eustress” (“good stress”) solely in terms of pathologic outcomes is circular and therefore unproductive

scientifically. One can conceive of a non-circular definition of eustress that is a kind of mirror image of the non-circular definition of distress. Just as distress is consciously experienced, negatively reinforcing, motivates escape and avoidance behavior, and enhances vigilance, eustress is consciously experienced, positively reinforcing, motivates approach and appetitive behavior, and enhances attention to oneself. Both distress and eustress have offered survival advantages in evolution, but either can be pathogenic in the setting of modern humanity. That is, neither may be only good or only bad for health. Just as modern-day pathologic consequences of distress are thought to include panic/anxiety, melancholic depression, or post-traumatic stress disorder, pathologic consequences of eustress might include drug and alcohol abuse, sex offenses, gambling and other risk-taking behaviors, and over-eating.

With repeated exposure to a stressor, the magnitude of the response decreases. Habituation is a characteristic of even primitive animals. The term, “dishabituation,” is used to refer to a return to the initial magnitude of response after habituation has taken place. A related phenomenon is exaggerated responsiveness of adapted organisms to a novel (“heterotypic”) stressor.

Organisms can protect and repair themselves after stress and even learn to anticipate and proactively make “feed-forward” adjustments that mitigate damage from future stress exposures. The concept is emerging that certain aspects of lifestyle, such as exercise training and some psychological interventions, enhance resilience. There is evidence that repeated exposures may increase resilience to heterotypic stressors.

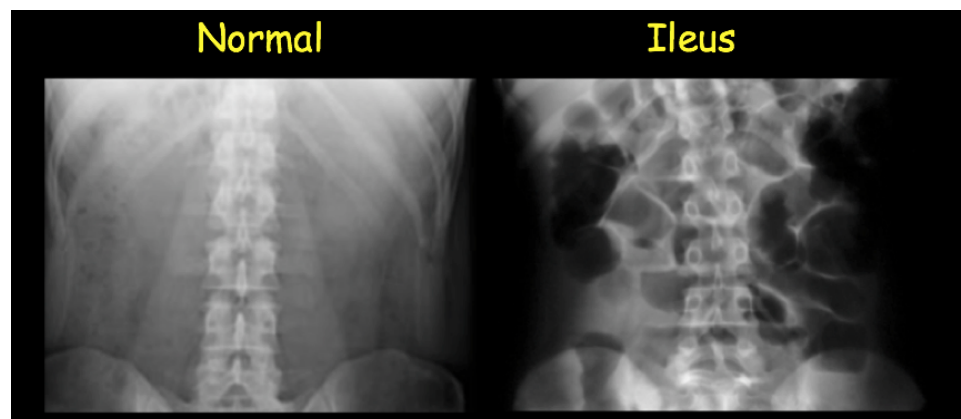
DISTRESS MADE STICKY

Biblical Lie Detection

The Bible contains a unique and remarkable instance of trial by ordeal and “lie detection”—actually distress detection.

Adrenaline produces marked effects on many body functions. These effects have been recognized throughout human history.

This was in the case of a woman accused by her husband of adultery. She would be brought to the priest, who would conduct the trial according to a specific ritual.

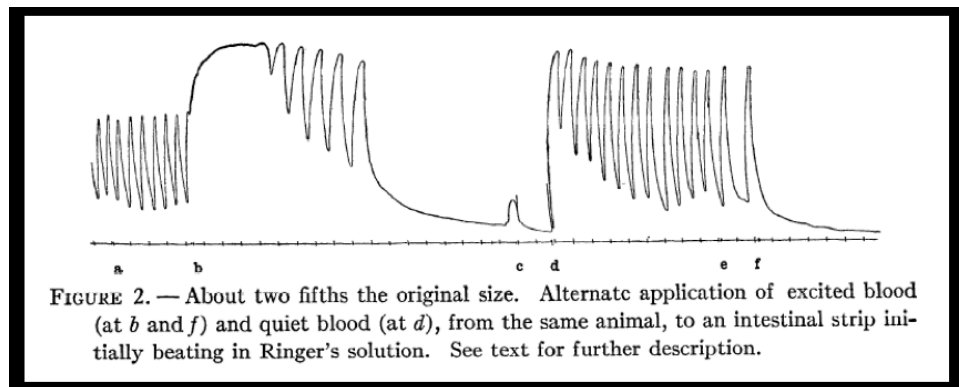


Abdominal distention from dilation of loops of bowel by air

The key sign of guilt was when the accused woman was forced to drink “waters of bitterness,” consisting of water and dust from the floor of the tabernacle. The priest would incant, “If

thou has gone aside, being under thy husband, and if thou be defiled . . . this water that causeth the curse shall go into thy bowels, and make thy belly to swell, and thy thigh to fall away” (Numbers 5:19-21). The accused woman would reply, “Amen, Amen” (the first use of the term in the Bible). The woman would then drink the test potion. If she had been unfaithful, her belly would swell.

Why would abdominal distention be a sign of distress and therefore, in biblical lie detection, of guilt? Adrenaline potently relaxes smooth muscle of the gastrointestinal tract. Indeed, this relaxation provided the basis for the first successful method, introduced by Walter B. Cannon, for detecting adrenaline release during emotional distress.



Cannon's demonstration of relaxation of an intestinal strip upon application of blood from a cat exposed to a barking dog—the first published evidence for adrenaline release during distress.

Cannon drew blood from a cat exposed to a barking dog. This evoked release into the cat's blood of a substance that relaxed a strip of gut tissue. Exposure of the strip to blood from the adrenal veins produced the same relaxing effect, and tying off the adrenal veins eliminated the effect, indicating that distress

released a substance from the adrenal glands into the bloodstream.

The woman would have a form of functional ileus (decreased propulsion of gut contents). In this setting, a non-palatable liquid would not pass through the gut, and the belly would swell.

It is not widely appreciated that high circulating levels of catecholamines can produce ileus. The distended loops of bowel would result in abdominal swelling. Ileus can even be an initial manifestation of pheochromocytoma, a tumor that secretes catecholamines into the bloodstream.

What would be the meaning of the guilty woman's thigh "falling away"? If the accused woman were innocent, she would be able to "retain seed." This might mean she would be able to conceive. It is well known that in distressing circumstances women can have anovulatory periods or stop menstruating. Both of the key signs of guilt in the biblical trial by ordeal therefore can be understood in terms of bodily effects of distress.

The 23rd Psalm

Psalm 23, a triumph of literature, has the core concept of calm confidence, because "The Lord is my shepherd..."

Right in the middle of the psalm is the well known verse, "Yea, though I walk through the valley of the shadow of death, I fear no evil: for thou art with me; thy rod and thy staff they comfort

me. Thou preparest a table before me in the presence of mine enemies...” What does setting a table in the presence of one’s enemies have to do with the theme of the psalm?

As you just learned, adrenaline decreases the ability of gut smooth muscle to contract. Given the inability to digest during distress, if you were able to eat in the presence of your enemies, you could not be distressed. The passage about setting a table in the presence of enemies therefore fits with the theme of the psalm: Because the “Lord is my shepherd . . . I fear no evil.”

Several instances occur in the Old Testament narrative in which a distressed individual cannot eat. Aaron is unable to eat the sacrifice, his priestly duty, after witnessing his sons’ death. Hannah cannot eat when tormented by her nemesis Peninah. Jonathan eats no food after Saul obsesses about David. Ahab does not eat out of jealousy of Elijah. Job in his suffering “abhorreth bread, and his soul dainty meat” (Job 33:20).

A Chicken with Its Head Cut Off

You probably have heard the phrase, “running around like a chicken with its head cut off.” If you were to chop off a chicken's head, wouldn’t the blood spurt out and the animal rapidly lose consciousness and become motionless?

Actually, no. A remarkable amount of blood remains in the body, as the severed trunk oozes blood. If you guillotined a laboratory rat, it would shriek for several seconds. To obtain “trunk blood,” you might have to squeeze it out!

Adrenaline's actions explain this macabre scene. Chopping off an animal's head instantly evokes drastic release of catecholamines into the bloodstream by the adrenal gland. So much adrenaline pours out, so fast, that "trunk blood" obtained immediately after decapitation contains about a hundred times the resting concentration of adrenaline. The surge of adrenaline constricts blood vessels and promotes platelet plugging to such an extent that chickens actually do run around with their heads cut off.

When adrenaline was patented about the turn of the 20th century, the drug's main intended use was to control bleeding. It is worth keeping in mind that in the setting of a heart attack due to a blood clot in a coronary artery, the associated emotional distress, resulting in adrenaline release, could be lethal by evoking a positive feedback loop. Because the class of drugs called benzodiazepines inhibit adrenaline release, treatment with a benzodiazepine may be considered for patients with acute myocardial infarction who manifest signs of emotional distress.

No Sweat

Not only the sympathetic cholinergic system (SCS) but also the sympathetic adrenergic system (SAS) contributes to emotional sweating.

Several years ago our Nurse Practitioner was going out for the evening and gave instructions to the babysitter. Her daughter had frequent asthma attacks, and so her mother wanted to demonstrate how to use an EpiPen™ in case there was an

emergency.

For practice she had a dummy pen, which could be reset by clicking the top—somewhat like clicking the top of a ball point pen. She showed the babysitter how easy it is to use an EpiPen™ —just pull off the blue safety release and jab with the orange needle end against the outer thigh and hold it in place for about 10 seconds, to deliver the adrenaline. But when she jabbed herself, to her surprise she felt a sharp needle prick, which was odd for the blunt ended dummy pen; and when she pulled the pen from her thigh, she noticed that she couldn't reset the pen by clicking the top.

That was when she felt a wave of sweat spread over her body. Within several seconds her clothes became drenched. She also noticed hyperventilation and jitteriness and realized that instead of a dummy pen she had used a real EpiPen™ and had injected adrenaline into her leg.



An EpiPen™ delivers 3 mg of adrenaline over about 10 seconds.

When she left our group for another position, as a going-away gift she gave me an EpiPen™, which I keep on display in my

office.

Snow White

Pallor is probably the most obvious among the many effects of adrenaline as a hormone. The pallor results from constriction of blood vessels in the skin. Constriction of skin blood vessels minimizes blood loss from physical trauma and also promotes increased blood temperature by interfering with heat loss from the blood delivered to the skin's surface.

The blood vessel constricting action of adrenaline varies remarkably with the particular body organ. Just a few centimeters below the skin, in the skeletal muscle, adrenaline dilates the blood vessels. This dilation redistributes blood toward the skeletal muscle, as would be appropriate in preparation for a “fight or flight” response.

I carried out an experiment once that involved infusion of adrenaline into the brachial artery of normal volunteers. The brachial artery carries the blood to the forearm and hand. The infusion produced obvious pallor of the hands, yet forearm blood flow, which is determined mainly by the blood vessels in skeletal muscle, actually increased in some people.

Adrenaline also constricts blood vessels in the gut and kidneys. In contrast, adrenaline exerts relatively small direct effects on the blood vessels in the heart muscle, the lungs, and the brain. Adrenaline’s net effect on the distribution of the blood ejected by the heart therefore is to shunt blood away from the skin and toward skeletal muscle while maintaining blood flow to the three vital organs.

Adrenaline-induced pallor is an instinctively communicated sign of terror. You turn “white with fright” and look “pale as a ghost.” You seem “ashen,” “wan,” and “pallid,” indicating not only pallor but also sickliness. Your skin becomes “pasty,” and you “blanch” as the “color drains from your face.”

I think this is why waving a white flag is a universal sign of surrender. Terrorized people display their open palms to the adversary, as if submitting for inspection and confirmation physical evidence for the absence of aggressive intent. Although it is true that you can become “livid” with rage, more likely you “burn” or “seethe,” the skin flushing hot rather than blanching cold. When enraged you “see red,” not white. I understand that in Chinese, the calligraphic characters that together mean “fear” literally denote “white face.”

In the Old Testament, Moses and Miriam, brother and sister, both turn “white as snow” in separate episodes when confronted directly by God. Miriam’s sudden pallor could have indicated an involuntary, automatic, instinctively communicated sign of terror. That sign would result from constriction of blood vessels in the skin, and the constriction would result from the local action of adrenaline.

At the same time and for the same reason that the skin becomes pale under the influence of adrenaline, the skin also turns cold. When the blood vessels in the skin constrict, delivery of blood to the skin decreases. Because the arteries carry blood to the skin, the largest organ of the body, at the core temperature, which typically exceeds the ambient temperature, the

temperature of the skin falls toward that of the cooler environment. You develop “cold feet.”

People withdrawing suddenly from an addictive drug go “cold turkey.” The origin of this phrase is obscure. Perhaps it refers to simultaneous constriction of skin blood vessels and development of goosebumps, both of which are produced by adrenaline as a hormone and by locally released norepinephrine as a neurotransmitter.

Tremulousness is another instinctively communicated sign of fear to the point of panic, appreciated by writers since ancient times. The Old Testament contains several instances of trembling as a sign of emotional upset. For instance, Isaac trembles as an automatic, immediate response when he realizes that he has been deceived by Jacob into giving his paternal blessing to Jacob, not Esau. Both adrenaline released from the adrenal gland and norepinephrine released from sympathetic nerves can produce this ineffectual, rhythmic skeletal muscle contraction. To “shudder,” “quiver,” “quake,” and “quail” not only mean to tremble but to do so in fear or uncertainty. I have observed that people receiving an infusion of yohimbine, which releases norepinephrine from sympathetic nerves and adrenaline from the adrenal gland, can have such severe trembling of the jaw that the teeth chatter.

Trembling and shivering during distress both probably reflect activation of the sympathetic noradrenergic system, since, as Cannon first showed, surgical inactivation of the adrenal glands augments, rather than prevents, shivering of animals exposed to cold. Perhaps predictably, patients with benign essential tremor

can obtain relief by treatment with a beta-adrenoceptor blocker, which attenuates some of the effects of both norepinephrine and adrenaline.

Musicians with stage fright or performance anxiety often take a beta-blocker before concerts. A friend of mine who is a professional cellist once told me that not only did several of his colleagues take a beta-blocker prophylactically before a concert but also that he could tell when they had done so. The performance would be technically accurate but with a subtle emotional restraint and detachment.

StressDots

StressCards, StressDots, StressRulers, BioDots, StressPens, StressPoints, StressControl cards, and similar items all include a shiny black patch of plastic. You press a fingertip on the patch for a minute or so, and the color changes. Depending on the color, you are “stressed,” neutral, or relaxed. You are supposed to try to change the color to that corresponding to being relaxed.

These items work by the same principle. The key is the liquid crystal patch or dot, which changes color as the temperature changes. When you learn to control your “stress,” you really learn to increase your skin temperature—a kind of biofeedback.

Why should skin temperature provide a gauge of stress? When you are distressed, you release adrenaline into the bloodstream.



Adrenaline decreases skin temperature.

The bloodstream delivers adrenaline to all organs of the body, and adrenaline tightens blood vessels in the skin. When the skin blood flow decreases due to blood vessel constriction, the skin temperature falls toward that of the usually much cooler room temperature. The card reports that you are “stressed.”

An Amazing Cooking Experiment

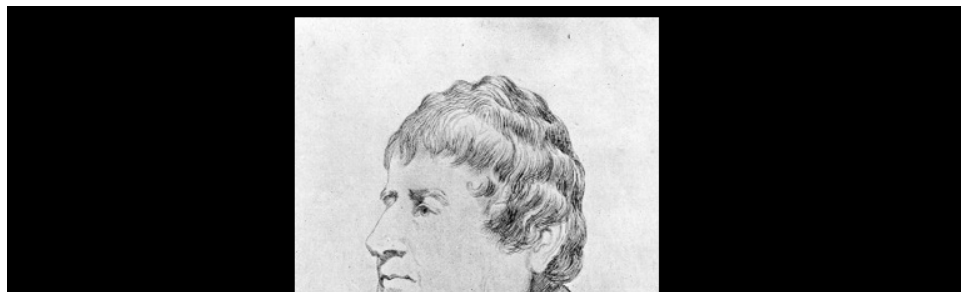
For the body to operate effectively requires maintaining the blood temperature within a fairly narrow range. Your body contains a temperature regulating system that is more efficient than that found in any man-made HVAC system. The brain keeps the blood temperature, or core temperature, about the same, by regulating activities of multiple effectors.

The “thermostat” in your brain receives temperature information from two sources. The first source is temperature sensors in the skin, a key interface between the outer and the inner worlds. A second source is sensors within the substance

of the brain itself that monitor the temperature of the blood. This duality corresponds to the two main determinants of heat dissipation and heat generation in the body — evaporative loss of heat from the skin's surface and generation of heat by internal metabolic processes.

Losing body heat efficiently requires sweating, and activation of a particular component of the automatic nervous system, the sympathetic cholinergic system (SCS), stimulates thermoregulatory sweating. Losing body heat by evaporative heat loss also requires delivering blood to the skin surface, so that the warm blood can equilibrate with the cool outside temperature. Inhibition of nerves supplying the skin in another component of the automatic nervous system, the sympathetic noradrenergic system (SNS), relaxes the local blood vessels, distributing the blood to the skin surface.

On January 23, 1774, the amazing ability of the human body to maintain core temperature by evaporative heat loss was demonstrated experimentally for the first time. Five men, including Dr. Charles Blagden, 26 years old at the time, entered a room that was heated progressively with dry air. Eventually the temperature exceeded that of boiling water, and an egg in the chamber roasted solid. The temperature of Blagden's exhaled breath was relatively cool compared with the external temperature in the room. He noted, "Whenever we breathed on a thermometer the quicksilver sank several degrees." Three weeks later, Blagden reported his observations to the Royal Society of London, which published his report in its Proceedings in 1775.



Sir Charles Blagden (1748-1820)

In the heat chamber Blagden eventually began to experience anxiety. His pulse rate increased dramatically, and he decided to end the experiment. He wrote, that at 260 degrees “I sweated, but not very profusely. For seven minutes my breathing continued perfectly good; but after that time I began to feel an oppression in my lungs, attended with a sense of anxiety; which gradually increasing for the space of a minute, I thought it most prudent to put an end to the experiment, and immediately left the room. My pulse, counted as soon as I came into the cool air, was found to beat at the rate of 144 pulsations in a minute, which is more than double its ordinary quickness.”

Adrenaline potently constricts blood vessels in the skin. This is part of the reason adrenaline increases the generation of metabolic heat. One may speculate that this amazing cooking experiment ended when the adrenaline level in Blagden’s bloodstream reached a high enough value to constrict the blood vessels in his skin. Increased heat production and decreased

evaporative cooling would then have increased the core temperature, producing distress and further adrenaline release. In other words, a positive feedback loop may have forced Blagden to call it quits.

Blagden had an illustrious career as a chemist. His notion of a chemical reaction was a founding concept of modern chemistry. His discovered that adding a solute such as table salt to water decreases the freezing temperature of the solution has been called Blagden's law.

Sweet Urine

The seventeenth century English physician Thomas Willis may have been the first scientist to note that patients with diabetes excrete sweet urine. The sweetness results from high blood levels of glucose, which is a sugar.

Injection of adrenaline increases the blood glucose level by releasing glucose into the bloodstream by the liver, accelerating the production of glucose from its storage form, glycogen, and inhibiting the release and actions of insulin.

Adrenaline is one of the three main hormones that regulate blood glucose levels, the other two being insulin and glucagon.

Claude Bernard, the originator of the concept of the inner world, first showed that glucose in the bloodstream is derived not from dietary intake of sugar but from its production within

body organs. It was Bernard who first isolated “glycogen” (from the Latin for “generator of sugar”) from liver tissue and demonstrated its conversion to glucose in the liver.

Puncture Diabetes

Bernard wondered whether release of glucose from the liver into the bloodstream is mediated by nerves supplying the liver. He found that stimulating the vagus nerve, however, produced no effect on blood glucose. In 1849 he conducted an experiment in which he punctured the spot in the brainstem from which the vagus nerve emanated. This did produce hyperglycemia, and within an hour the urine contained abundant sugar. Diabetes by piqûre, or puncture, has been associated with Bernard's name ever since.

Bernard thought that he had discovered a neuronal cause of diabetes. To demonstrate that trauma to the floor of the fourth ventricle released glucose from the liver by way of the vagus nerves, he cut them before the puncture. Unexpectedly, the puncture still produced hyperglycemia, and he had to reject the notion of diabetes from vagus nerve stimulation.

Bernard then pursued other ways the nervous system might contribute to the release of glucose by the liver. He found that cutting the spinal cord just above the site of exit of the splanchnic nerves, which carry pre-ganglionic fibers of the sympathetic adrenergic system to the adrenal glands, did abolish the increase in blood glucose levels consequent to puncturing the floor of the fourth ventricle. From this finding he inferred that piqûre diabetes results from stimulation of

sympathetic nerves supplying the liver. This was before the discovery of the sympathetic nervous supply of fibers to the adrenal gland. Piquê diabetes probably mainly results from the effects of adrenaline released into the bloodstream, although sympathetic nerves to the liver may also contribute.

Decades later, deficiency of insulin was shown to be the culprit in juvenile-onset diabetes; however, ironically, modern research about insulin resistance in adult-onset diabetes has returned to the concept, based on Bernard's experiment, that the brain does play a role.

A Waist is a Terrible Thing to Mind

Injected adrenaline evokes several effects that taken together rapidly mobilize metabolic fuels from storage sites and burn calories. The rate of metabolism in the body as a whole increases; oxygen consumption by the heart increases; body temperature increases; stores of glycogen in the liver are broken down into the metabolic fuel, glucose; and fats are converted to free fatty acids, generating heat in the process.

Several effective weight loss drugs share the effect of augmenting occupation of receptors for catecholamines, both inside and outside the brain. Amphetamines such as phentermine increase release and inhibit reuptake of catecholamines, suppress appetite and increase metabolic rate. Phentermine, prescribed with fenfluramine, constituted "Fen-Phen," which, while effective in promoting weight loss in dieters, produced harmful heart and lung side effects. Phenylpropanolamine (PPE), another sympathomimetic amine,

was the active ingredient in many over-the-counter weight loss drugs, until PPE was also removed from the market.

Conversely, treatment with beta-adrenoceptor blockers, which inhibit adrenaline effects, can promote weight gain. Studies have indicated a statistical association between polymorphisms of beta-adrenoceptor subtypes and obesity; and weight loss drugs are being tested that work by stimulating particular beta-adrenoceptor subtypes.

An Unusual Weight-lifting Feat

Many years ago, the *Guinness Book of World Records* section on weight lifting contained the following entry, “It was reported that a hysterical 123-lb. woman, Mrs. Maxwell Rogers, lifted one end of a 3,600-lb. car which, after the collapse of a jack, had fallen on top of her son at Tampa, Florida, on April 24, 1960. She cracked some vertebrae” (*Guinness Book of World Records*, 1976, 669). Apparently, Mrs. Rogers had tapped automatically into what Cannon have called “reservoirs of power.”

Some of Cannon’s papers described direct effects of adrenaline in augmenting the force of skeletal muscle contraction or in antagonizing the fatigue effect of continual trains of electrical stimulation-induced excitation of skeletal muscle contraction. Researchers seem to have doubted and certainly subsequently lost interest in the direct effects of adrenaline in augmenting contraction of skeletal muscle and preventing skeletal muscle fatigue. But all would agree that emotionally distressing situations, such as that encountered by Mrs. Maxwell,

temporarily enable people to perform extraordinary feats of strength and speed. Because these behaviors are automatic, involuntary, and unconscious, they probably importantly involve the autonomic nervous system.

In his *Expression of the Emotions in Man and Animals*, Charles Darwin noted the self-reinforcing, energizing effect of emotions. He wrote, “The excited brain gives strength to the muscles, and at the same time energy to the will...Anger and joy are from the first exciting emotions, and they naturally lead, more especially the former, to energetic movements, which react on the heart and this again on the brain.”

In the early 1960s, the psychologists Stanley Schachter and Jerome Singer, of Columbia University, studied effects of adrenaline on the intensity of emotional experiences. The investigators injected adrenaline into healthy subjects and either informed them correctly or misinformed them about what the side effects of the injected drug might be. Then they exposed the subjects to situations that would provoke annoyance or amusement. The subjects who had been informed correctly about the side effects of the injection did not report feeling more emotional than the subjects who had received an injection of a placebo; however, the subjects who had been misinformed reported feeling more emotional, with more anger or elation depending on the cognitive circumstances, than did the subjects who been informed correctly about what the injection would do. These findings supported the view that the intensity of emotional experience, whether negative or positive, is greater when people sense physiological activation and do not have an explanation for that activation besides the emotional

experience. That is, both physiological arousal and cognitions consonant with an emotion determine the intensity of experienced emotion.

It would not be a big leap to propose that the more intense an emotional experience, the greater the amount of involuntary, automatic, unconscious augmentation of the behavioral concomitants of that experience. If adrenaline amplified and prolonged rage, for instance, and rage involuntarily contracted skeletal muscle of the limbs, then adrenaline could augment skeletal muscle contraction and delay the onset of fatigue, even without a direct effect on the skeletal muscle.

A Little Pain Can't Hurt

We all know that emotion-related feats of strength and speed are associated with remarkable loss of the sensation of pain. This is called “stress-induced analgesia.” Pain causes adrenaline release from the adrenal gland, as Cannon showed about a century ago. A difficult question—which remains incompletely answered—is what if anything does adrenaline or any other member of its chemical family have to do with the perception of pain?

Adrenaline or norepinephrine may alter the experience of pain by occupying alpha-2 adrenoceptors in the spinal cord. These receptors appear to contribute to a “gate” for transmitting pain impulses up to the brain. The source of the chemical transmitter that would occupy these alpha-2 adrenoceptors may not be circulating adrenaline, or even norepinephrine released as a neurotransmitter from sympathetic nerves, but

norepinephrine released from nerves that project from the brainstem to the spinal cord. The locus ceruleus, a small cluster of cells in the back of the pons, is the main source of norepinephrine in the brain. Locus ceruleus cells send widely branching fibers throughout the brain, probably contributing to psycho-emotional phenomena such as vigilance and the memory of distressing events. It is unclear whether locus ceruleus neurons are the source of the norepinephrine that modulates the transmission of pain impulses.

The main known modulators of pain sensation are endogenous opioids. Behaviors such as exercise increase occupation of opioid receptors in the brain, explaining the sense of elation some people feel after a workout. In response to painful stimuli, the brain releases opioids that apparently limit the severity of experienced pain, because blockade of opioid receptors augments the amount of pain for a given amount of stimulation. Blockade of opioid receptors also augments the release of adrenaline. Finally, stimulation of the adrenal gland releases not only adrenaline but also endogenous painkiller opiates called enkephalins.

Before dental surgery, dentists often include adrenaline in the local anesthetic, not only because this decreases bleeding but also because it prolongs the anesthesia time. Injection of adrenaline with the local anesthetic always produces large, physiologically active increases in circulating adrenaline levels. Adrenaline injection actually inhibits, rather than augments, responses of circulating levels of the opioid, beta-endorphin, in the setting of wisdom tooth extraction. How and why injection of adrenaline would inhibit the opioid response is unknown.

A Famous Photo

One of the most famous and haunting photographs ever published appeared on the cover of *National Geographic* in June, 1985. Taken by Steve McCurry, it was entitled, “Afghan Girl.” My guess is that you’ve seen this photo and remember being struck by the girl’s freaky stare with pinpoint pupils.

(I wanted to include “Afghan Girl” in this book, but the magazine wouldn’t allow me to modify the photo for teaching purposes. In the drawings below I try to convey the point.) The pairs of eyes in the two drawings are identical, except for two aspects. First, the pupils of the eyes on the left are severely constricted (miosis). Second, the eyelids of the eyes on the left are raised. This is what happens when a person is startled. The



Believe it or not, the eyes in these drawings are identical, except for the constricted pupils and raised eyelids in the eyes on the left. This combination gives one the impression of an eerie stare.

combination of miosis and raised eyelids produces a penetrating, glaring stare.

An alternative explanation for miosis in the “Afghan Girl” might be an opiate. Opiates such as morphine and heroin produce miosis, probably via stimulation of neurons in the

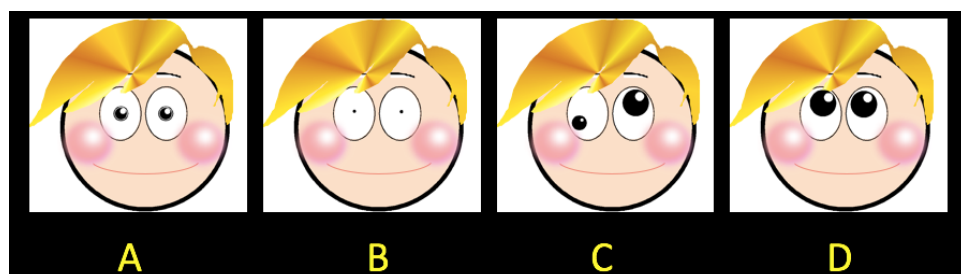
Edinger-Westphal nucleus in the back of the midbrain.
Afghanistan has been the world's most prolific producer of illicit opiates. At the time of the photo, during the war in Afghanistan against the Soviet occupation, the girl was living in a refugee camp in Pakistan. An opiate, however, would not explain the raised eyebrows.

In an interview many years later the photographer recalled that the girl had been in school at the time. At first she had covered her face with her hands, but her teacher told her to take her hands down and let him take her picture because of the importance of their story. When the shutter was released, the girl had just uncovered her face. In other words, the pupillary light reflex could have contributed to the miosis. To me, though, there was an element of startle because of the raised eyebrows. I would imagine that if the miosis reflected only a pupillary light reflex, she would have squinted.

Students of Pupils

Cartoonists frequently exploit effects of alterations in autonomic nervous system outflows to the pupils to convey the psychological state of the characters.

Look at the four cartoon faces. One of them is neutral, one is cute and sweet, one is disoriented, and one is startled. Which is which?



Cartoonists have long exploited different appearances of the pupils to convey different neurobehavioral states.

The answers seem intuitively obvious: (A) is neutral, (B) is startle, (C) is disorientation, and (D) is cute.

When I've asked doctors the same question, they often get it wrong, because of what they have been taught about the "stress response." Based on Cannon's fight-or-flight response and the emergency function of the "sympathoadrenal system," distress raises adrenaline levels and increases sympathetic nervous system outflows, and these changes would produce dilation of the pupils (mydriasis). By this rationale doctors can go against their own intuition and guess that (D) corresponds to startle.

Mydriasis attending distress takes time, however. Recall that the sympathetic post-ganglionic nerves are non-myelinated and conduct signals relatively slowly. The reflex pathway is relatively long, because the sympathetic nerves to the head emanate from the thoracic spinal cord, not the brainstem like parasympathetic nerves. The immediate startle response involves miosis, probably because of more rapid effects of parasympathetic nervous system stimulation.

The vagus nerves, which convey parasympathetic nervous system signals to the heart from each side of the lower brainstem, are also myelinated and conduct signals rapidly.

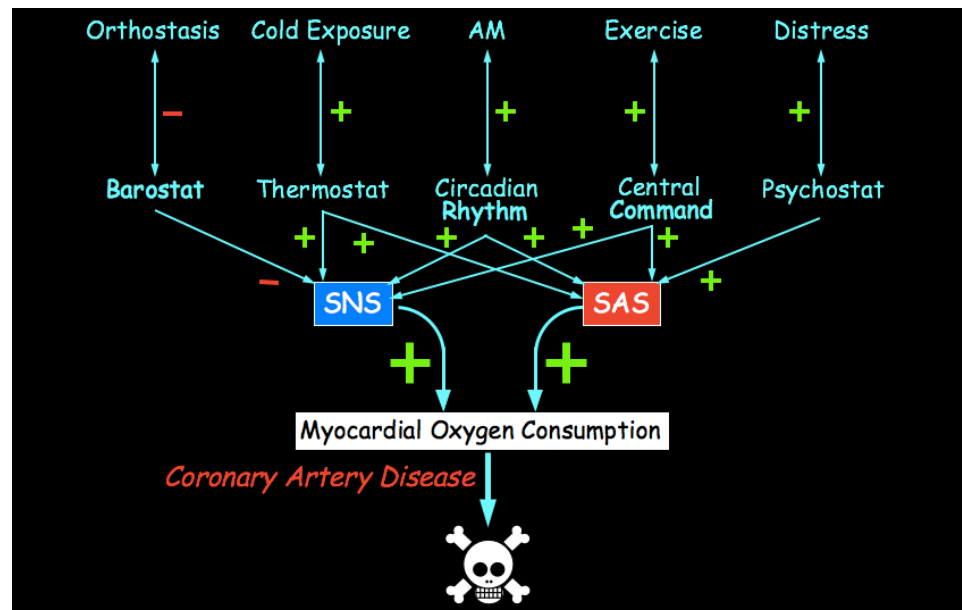
Sudden vagal stimulation during startle would be expected cause a rapid drop in heart rate or a brief period of a type of heart block from slowed conduction of electrical signals within the heart. This is why when you are startled you feel that your heart has “skipped a beat.” Startle precedes the experience of distress, and the bradycardia or heart block caused by vagal activation precedes the fast and pounding heartbeat resulting from sympathetic noradrenergic and adrenergic system stimulation.

Doctors are also taught, in this case correctly, that a “blown,” dilated pupil on one side and deviation of the eye on that side can disclose a catastrophe inside the head, such as from a clot on the brain. I think cartoonists exploit the instinctive communication value of this appearance to convey disorientation or delirium, as in panel (C).

WHAT ARE DYSAUTONOMIAS?

IN DYSAUTONOMIAS WHAT GOES WRONG?

“Dysautonomia” refers to a condition in which altered functions of one or more components of the autonomic nervous system adversely affect health.



In coronary artery disease, what normally would be appropriate changes in autonomic functions can be lethal. This is an example of a dysautonomia from worsening of an independent pathological state.

Probably the most common type of dysautonomia involves compensatory, normal autonomic nervous system responses that worsen an independent disease process, rather than involving an abnormality of the autonomic nervous system itself. A classic example is sudden death in an old man

shoveling snow. In a person with coronary artery disease, normal sympathetic noradrenergic and adrenergic system activation can incite a lethal positive feedback loop when myocardial oxygen consumption exceeds the supply.

Changes in activities of components of the autonomic nervous system can even be harmful when the changes compensate for abnormal functioning of a different body system. For instance, in heart failure, the heart fails to deliver an appropriate amount of blood to body organs. Among several compensatory adjustments, one is increased sympathetic noradrenergic system outflow to heart. This improves the pumping function of the heart; however, compensatory activation of the sympathetic noradrenergic system also promotes overgrowth of heart muscle, which can stiffen the heart walls and worsen the heart failure.

In other forms of dysautonomia, the problem is from abnormal functioning within the autonomic nervous system itself. This is the form of dysautonomia emphasized for much of the rest of this book.

“Dysautonomia” usually refers to a disorder of one or more components of the autonomic nervous system itself.

Autonomic nervous system failure occurs relatively commonly in diabetes, alcoholism, amyloidosis, AIDS, and cancer treatment with particular drugs. In several diseases, such as diabetes, the patients do worse in the long run if they have autonomic failure.

We know much more about what goes wrong with the sympathetic noradrenergic system (SNS) than with other parts of the autonomic nervous system in dysautonomias. Often it is difficult and sometimes impossible to determine whether the lesion is at the level of the autonomic nerves, the spinal cord, the brainstem, or higher structures.

In general, there are two ways dysautonomias can result from altered function of the SNS. The first is when the system is activated to take over when another system fails. This is called compensatory activation. The second is when there is an abnormality of the SNS itself. There are also two general ways that functions of the SNS can be abnormal. The first is underactivity and the second overactivity of the system. Both underactivity and overactivity of the SNS can be persistent and long-term or can be occasional and short-term—i.e., chronic or episodic.

An example of acute sympathetic noradrenergic failure is fainting associated with decreased sympathetic noradrenergic system outflow to skeletal muscle. An example of chronic sympathetic noradrenergic failure is neurogenic orthostatic hypotension associated with loss of sympathetic noradrenergic nerves. An example of acute sympathetic noradrenergic activation is paroxysmal hypertension due to increased sympathetic noradrenergic outflows in a patient with a hemorrhagic stroke. An example of chronic sympathetic noradrenergic activation is hypernoradrenergic hypertension.

The same 2 X 2 approach based on acute vs. chronic and failure vs. stimulation applies to other components of the autonomic

Four Types of Dysautonomia	
Autonomic Failure Acute	Autonomic Failure Chronic
Autonomic Stimulation Acute	Autonomic Stimulation Chronic

One approach to classifying dysautonomias is based on failure vs. stimulation and acute vs. chronic.

nervous system.

There is a difficulty with this sort of conceptual approach. Some dysautonomias involve abnormalities of specific components of the autonomic nervous system and not others. For instance, in dopamine-beta-hydroxylase deficiency, there is failure of the sympathetic noradrenergic system, due to the inability to synthesize norepinephrine, but other components of the autonomic nervous system are intact. In Sjogren's syndrome there seems to be a rather selective parasympathetic cholinergic lesion. In autonomically mediated syncope, the sympathetic adrenergic and parasympathetic systems are activated, whereas sympathetic noradrenergic system outflow (at least to skeletal muscle) can abruptly cease. Finally, Parkinson's disease involves prominent loss of sympathetic noradrenergic nerves in the heart, whereas sympathetic cholinergic function, as indicated by sweating, can be increased, normal, or decreased.

The concepts of “autonomic failure” and “autonomic hyperactivity” have limited usefulness, because some dysautonomias involve abnormal functions of specific components of the autonomic nervous system.

The Ironic Case of John Hunter

Normal changes in activities of the autonomic nervous system can be harmful or even lethal in the setting of an independent disease state.

For instance, in patients with coronary heart disease, what would otherwise be considered physiologic responses to emotional distress can provoke attacks of chest pressure (angina pectoris) and even sudden death. One of the earliest and best-documented—and surely the most ironic—illustrations of this phenomenon was the case of Dr. John Hunter, the renowned academic surgeon who is considered to be the father of experimental pathology in England.

His colleague, William Heberden, gave the first clear description of angina pectoris as a symptom of coronary artery disease. In March, 1775, Hunter performed an autopsy on one of Heberden’s patients who had died suddenly during a violent spell of anger. Hunter described coronary arteriosclerosis when he observed, “The two coronary arteries, from their origin to many of their ramifications upon the heart, were become one piece of bone.”

Hunter himself was notoriously prone to defensive argument, irrational outbursts, obstinance, and impatience—he might be called a “hostile Type A.” In 1785, Hunter began to experience the same angina pectoris that Heberden had described in the patient whom Hunter had autopsied. Hunter’s brother-in-law, Everard Home, wrote:

“...the first attack of these complaints was produced by an affection of the mind, and every future return of any consequence arose from the same cause; and although bodily exercise, or distention of the stomach, brought on slighter affections, it still required the mind to be affected to render them severe; and as his mind was irritated by trifles, these produced the most violent effects on the disease. His coachman being beyond his times, or a servant not attending to his directions, brought on the spasms, while a real misfortune produced no effect....”



Dr. John Hunter, from a portrait by Sir Joshua Reynolds

Home described eloquently the prolonged episodes of severe chest pain from which Hunter suffered. These episodes were accompanied by pallor followed by swooning:

“I was with him during the whole of this attack, and never saw anything equal to the agonies he suffered; and when he fainted away, I thought him dead...”

Heberden diagnosed Hunter with angina pectoris, and Hunter claimed, “My life is in the hands of any rascal who chooses to annoy or tease me.”

This proved to be one of the most ironic statements in the history of medicine. Here is why. In Home’s words, “On October 16, 1793, when in his usual state of health, he went to St. George's Hospital, and meeting with some things which irritated his mind, and not being perfectly master of the circumstances, he withheld his sentiments, in which state of restraint he went into the next room, and turning around to Dr. Robertson, one of the physicians of the hospital, he gave a deep groan and dropt down dead.”

The story — and irony — does not end here. Hunter’s body was then autopsied, and Home supervised the procedure. The examination confirmed the cause of Hunter’s death to be atherosclerosis. His myocardium was scarred, and his coronary arteries were so calcified that Home described them as “bony tubes.”

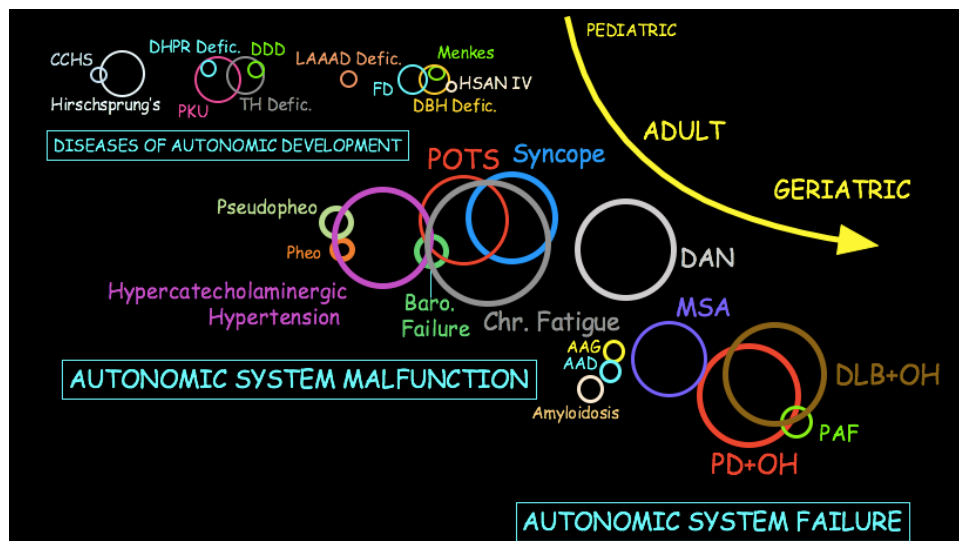
Bony tubes, but not tubes clogged with clot. Hunter did not die of a coronary thrombosis. He also did not die of congestive heart failure, which produces cardiac enlargement, since according to Home, “The heart itself was very small, appearing too little for the cavity in which it lay, and did not give the idea of its being the effect of an unusual degree of contraction, but more of its having shrunk in its size.”

Given Hunter's previous prolonged episodes of emotion-provoked severe chest pain accompanied by pallor and followed by faintness and collapse, one may speculate that adrenaline release in the setting of coronary artery disease incited a lethal positive feedback loop. That is, emotion evoked sympathetic adrenergic system activation. The adrenaline-induced increase in myocardial oxygen consumption was not balanced by an increase in oxygen supply because of the rigidified coronary arteries. The imbalance elicited angina pectoris. The angina pectoris exacerbated the distress and thereby the adrenaline secretion, precipitating a lethal arrhythmia.

WHEN IN LIFE DO DYSAUTONOMIAS OCCUR?

The Dysautonomias Universe

Different types of dysautonomia occur in the different stages of life.



The Dysautonomias "Universe." There are many forms of dysautonomia, which can occur at any age.

In infants and children, dysautonomias often reflect problems in the development of the autonomic nervous system.



Dysautonomias in the young often reflect genetic or developmental disorders of the autonomic nervous system.

Frequently the cause is a genetic change, a mutation.

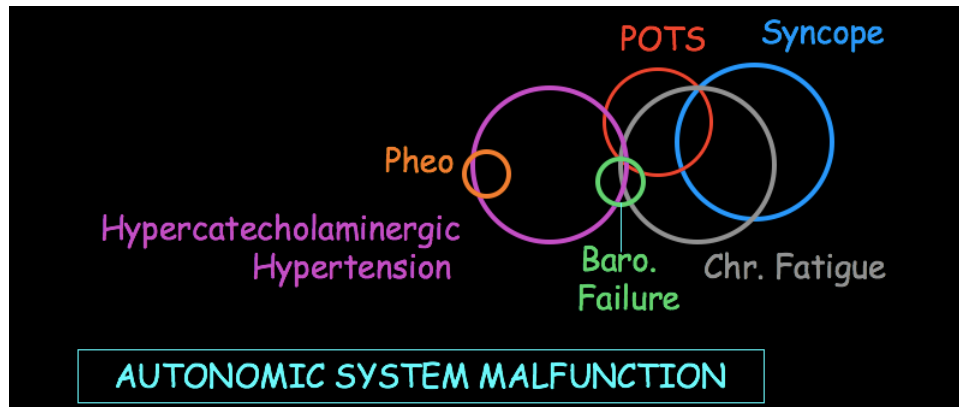
A mutation is like a “typo” in the genetic encyclopedia.

One type of mutation, found in people of Ashkenazi extraction, causes familial dysautonomia (FD). Another mutation produces dysautonomias in children because of a type of phenylketonuria (PKU). Another causes “kinky hair disease” (Menkes disease). There are also genetic diseases of proteins required for synthesizing or storing catecholamines. In general, dysautonomias from genetic mutations are rare.

In Hirschsprung’s disease, there is a lack of development of nerve cells of the enteric nervous system in the colon, usually without an identified mutation.

In adults, dysautonomias frequently involve inappropriate regulation of intact autonomic nerves. Examples are neurocardiogenic syncope (also called autonomically mediated syncope or reflex syncope), in which the person suffers from frequent episodes of fainting or near fainting; postural tachycardia syndrome, in which the person cannot tolerate

standing up for long periods and has a rapid pulse rate during standing; and hypernoradrenergic hypertension, in which overactivity of the sympathetic noradrenergic system causes a form of high blood pressure.

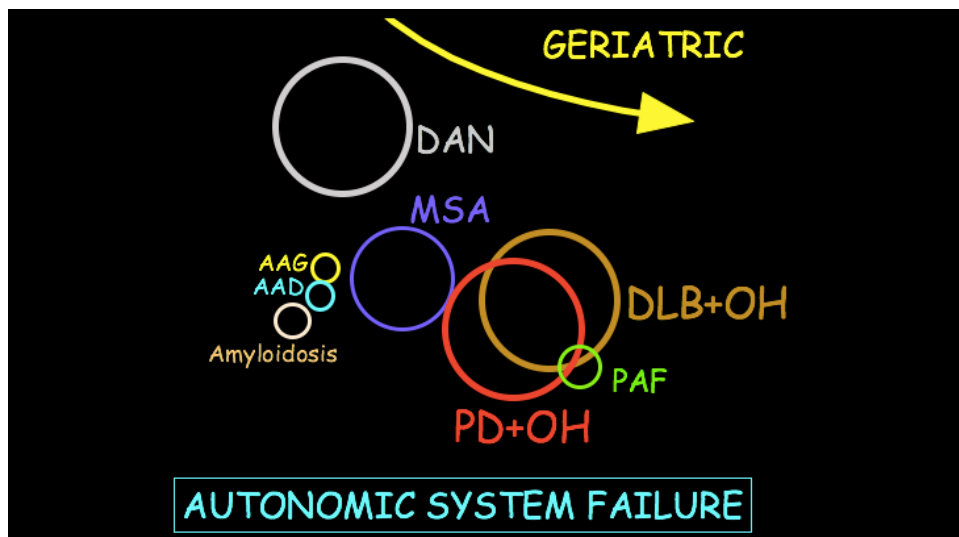


In adults, dysautonomias usually reflect functional changes in a generally intact autonomic nervous system.

In adults, dysautonomias usually reflect functional changes in a generally intact autonomic nervous system.

Dysautonomias in adults often are associated with—and may be secondary to—another disease process or a drug. Common secondary causes include medications, diabetes (diabetic autonomic neuropathy, or DAN), chemotherapy for cancer, irradiation of the neck, and alcoholism. Activities of components of the autonomic nervous system can change in an attempt to compensate for dehydration or low blood volume. A viral infection may impact the autonomic nervous system, or autonomic nerves may be subject to autoimmune attack, as in autoimmune autonomic ganglionopathy, or AAG.

Rarely, dysautonomias in adults can reflect genetic mutations. Examples are a rare form of postural tachycardia syndrome (POTS) that is associated with a mutation that decreases the ability to inactivate norepinephrine, the chemical messenger of the sympathetic noradrenergic system. Sympathetic noradrenergic failure can also result from a mutation of the gene that encodes dopamine-beta-hydroxylase (DBH), which is required to synthesize norepinephrine.



In the elderly, dysautonomias often result from neurodegeneration, loss of nerve cells in the brain or in the autonomic nervous system itself.

In the elderly, dysautonomia typically reflects a neurodegenerative disease. The degeneration may take the form of lesions in the central nervous system, as in multiple system atrophy, loss of autonomic post-ganglionic nerves, as in pure autonomic failure (PAF), or both, as in Parkinson's disease with orthostatic hypotension.

We will return to these dysautonomias later in more detail.

HOW ARE DYSAUTONOMIAS CLASSIFIED?

Dysautonomias can be mysterious and controversial, and doctors can disagree about the diagnostic classification of these disorders.

Doctors can disagree about how to classify dysautonomias.

As you read about dysautonomias, keep in mind that the particular labels given for many of these conditions are often best guesses. Such labels can refer to essentially sets of symptoms and signs without regard to causal mechanisms. Even with the same label, different people can have very different symptoms. Actual mechanisms for many of these conditions are not well understood. Hopefully, further research will lead to discoveries about pathogenetic mechanisms and to more informative names.

In many cases of dysautonomia, a specific diagnosis cannot be made.

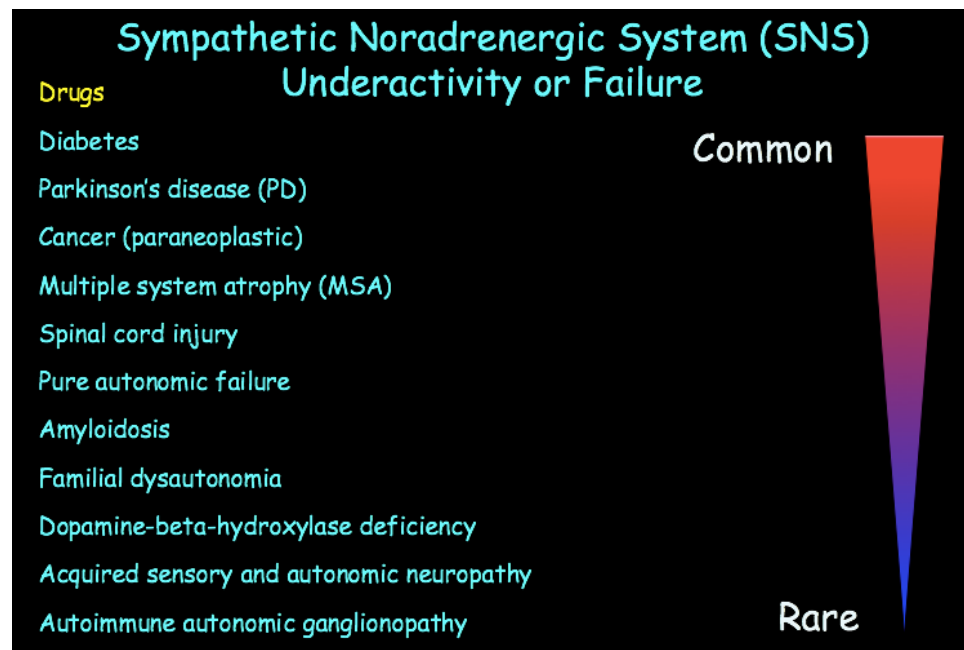
The primary concern for both the patient and the doctor should be symptom management, because effective symptom management provides relief and improves quality of life

Conditions Associated with Autonomic Failure

The autonomic nervous system has component sub-systems, which can be affected differently in different forms of dysautonomia. It is quite rare for the entire autonomic nervous system to fail as part of a disease process.

Underactivity of the entire autonomic nervous system as part of a disease is rare.

This section describes the symptoms and signs of underactivity of the sub-systems.



Probably the most common cause of underactivity or failure of the sympathetic noradrenergic system (SNS) is drugs.

Several drugs inhibit functions of the sympathetic

noradrenergic system (SNS). These include adrenoceptor blockers, tricyclic antidepressants, clonidine, and prednisone. Among diseases, diabetes probably is the most common cause of sympathetic nervous system underactivity. Primary causes of sympathetic nervous system failure such as familial dysautonomia and autoimmune autonomic ganglionopathy are rare. SNS failure may occur in the setting of a cancer or as a side effect of chemotherapy.

Probably the most common cause of underactivity or overactivity of the sympathetic noradrenergic system is drugs.

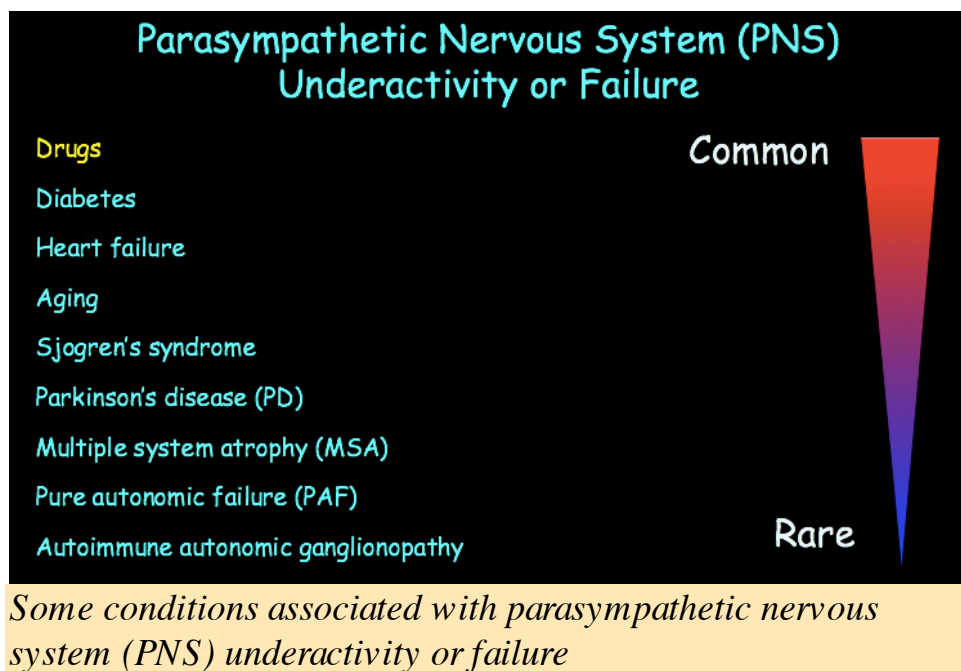
Sympathetic noradrenergic system (SNS) failure typically manifests as orthostatic hypotension (OH). SNS failure can also produce low blood pressure after eating a meal (post-prandial hypotension), after exercising, or upon exposure to warm temperature. The failure is associated with a tendency to have less than the normal increase in the force and rate of the heartbeat during exercise. This could manifest clinically as fatigue, shortness of breath with exercise, or exercise intolerance.

A fall in blood pressure when the patient stands (orthostatic hypotension) is an important sign of failure of the sympathetic noradrenergic system.

About 1/3 of patients with Parkinson's disease have orthostatic hypotension, and all such patients have a loss of sympathetic noradrenergic nerves in the heart. By definition, pure

autonomic failure patients have SNS failure.

The parasympathetic nervous system (PNS) is underactive in some common conditions, including heart failure, diabetes, and Parkinson's disease. PNS underactivity in these conditions probably reflects decreased neuronal outflow from the brainstem, rather than loss of parasympathetic nerves. These conditions can also feature SNS underactivity (diabetes is an example) or SNS overactivity (heart failure is an example). Parasympathetic nervous system functions tend to decrease also with normal aging.



When the parasympathetic nervous system is underactive, the person has a dry mouth (and consequently a raspy voice), constipation, a tendency to retain urine in the bladder, a relatively fast pulse rate, dry eyes, and, in men, erectile failure. Several drugs can cause these symptoms, such as drugs for

urinary incontinence or diarrhea.

Parasympathetic nervous system underactivity produces many symptoms, including dry mouth, constipation, urinary problems, decreased tear production, and (in men) inability to have an erection.

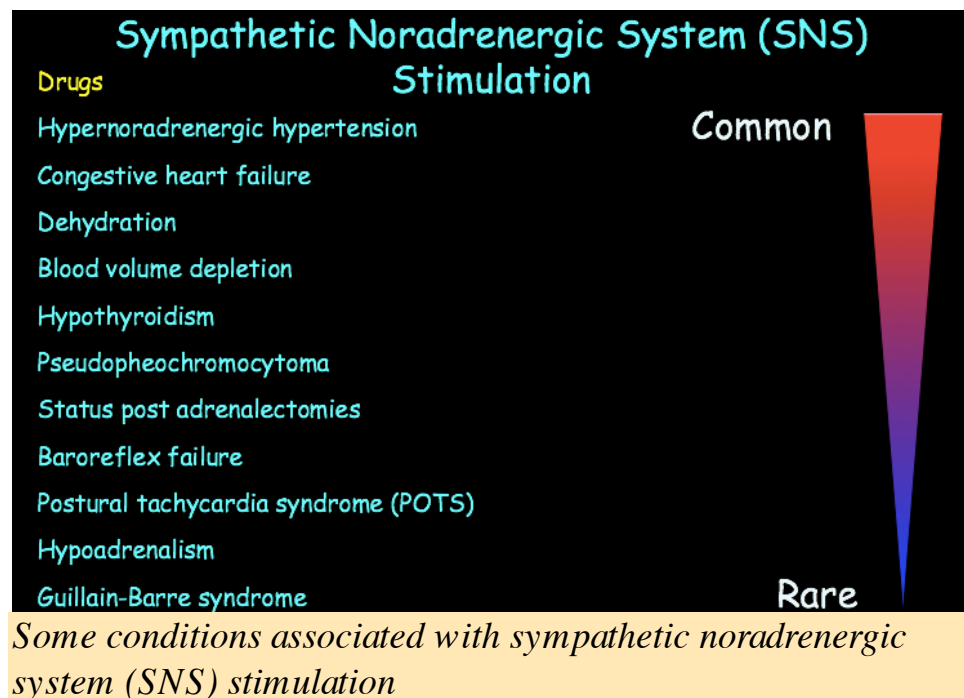
Since acetylcholine is the main chemical messenger used by the sympathetic nervous system for sweating, while norepinephrine is the main chemical messenger used by the sympathetic nervous system to tighten blood vessels and maintain blood pressure during standing, a patient with a specific problem in the production, release, or receptors for norepinephrine may have orthostatic hypotension and yet sweat normally.

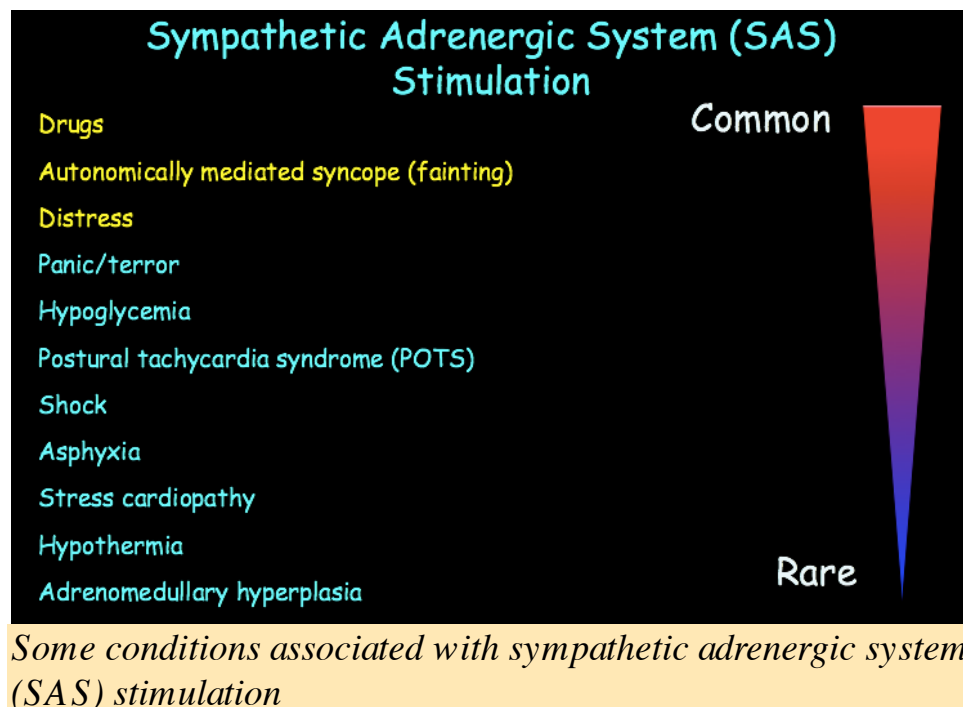
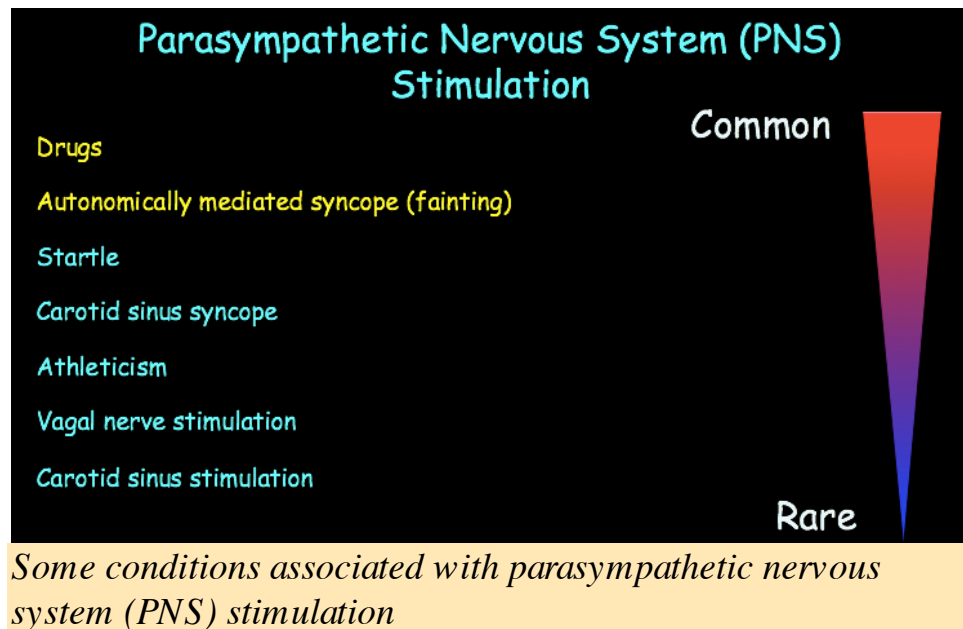
Sweating and blood pressure are “automatic” functions controlled by different chemicals.

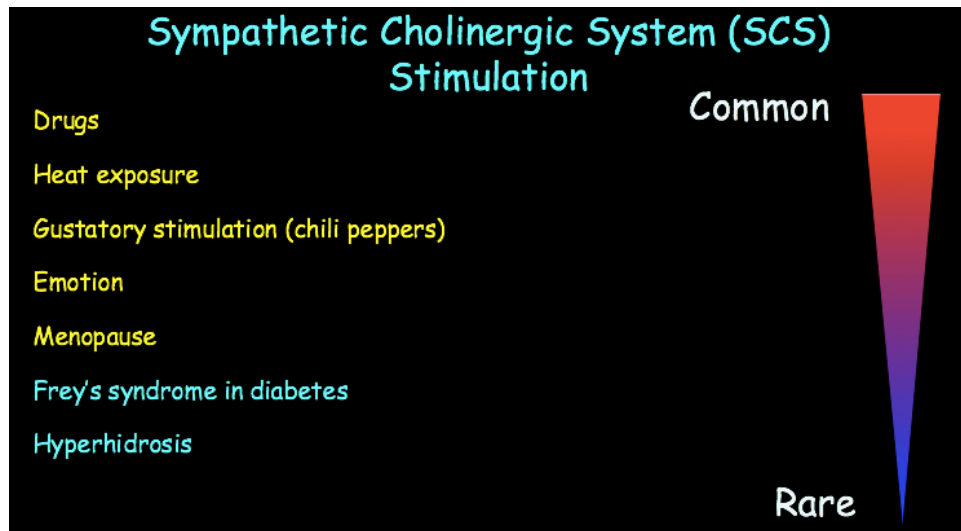
Unlike the parasympathetic cholinergic system and the sympathetic noradrenergic system, which play important roles in everyday activities such as digesting and standing up, the sympathetic adrenergic system is associated with responses to global metabolic challenges or threats to survival. When you are at rest, your adrenal glands release very little adrenaline into the bloodstream, and plasma adrenaline levels are so low that until relatively recently they were below the limit of detection of available assay methods. It is unclear if under resting conditions there are any symptoms from sympathetic adrenergic system failure.

Adrenaline is one of the body's main hormones for regulating blood levels of glucose, which is a key metabolic fuel. Hypoglycemia evokes profound increases in plasma adrenaline levels. Effects on the sympathetic noradrenergic system in this setting are subtler. Failure of the sympathetic adrenergic system therefore might be expected to cause a tendency to low glucose levels. In patients who have diabetes and take injections of insulin, failure or blockade of the sympathetic adrenergic system can result in susceptibility to prolonged hypoglycemia reactions to the insulin.

Conditions Associated with Autonomic Stimulation





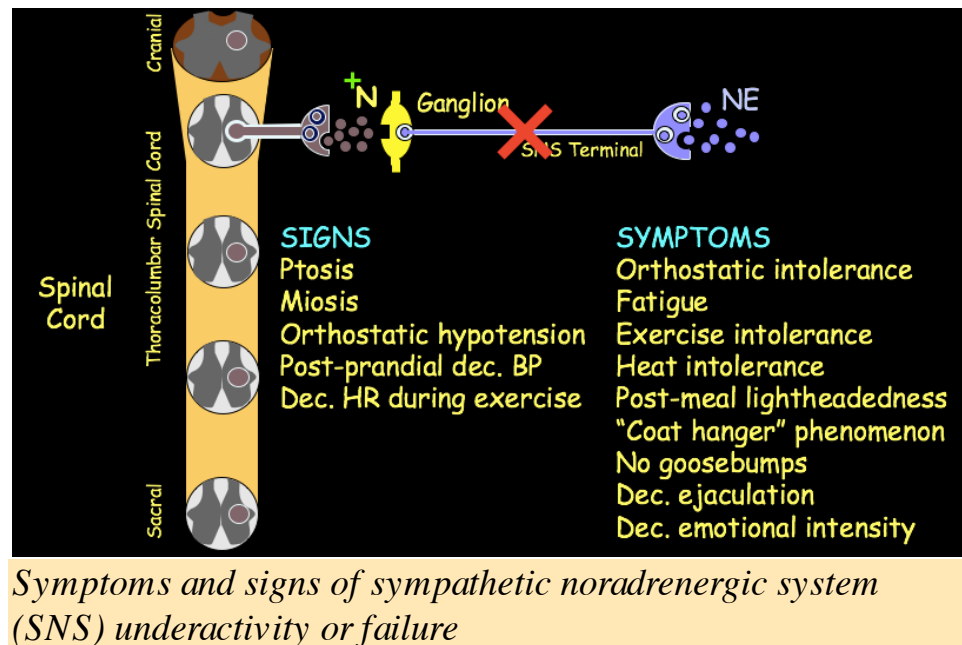


Some conditions associated with sympathetic cholinergic system (SCS) stimulation

What Are the Symptoms and Signs of Dysautonomias?

Symptoms and signs of dysautonomias result from alterations in activities of one or more components of the autonomic nervous system.

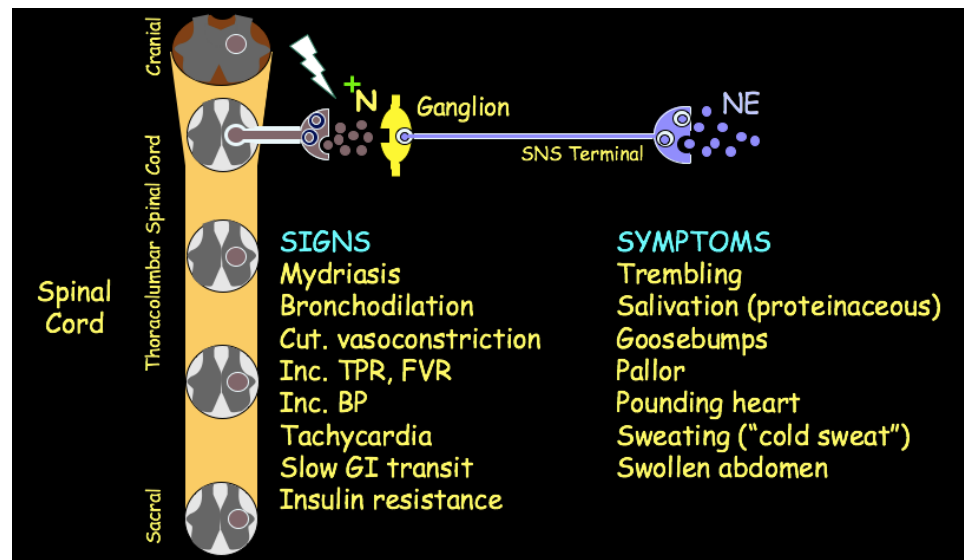
Activation or inhibition of the different components of the autonomic nervous system produces different effects on the body.



Symptoms of failure of the sympathetic noradrenergic system (SNS) include orthostatic intolerance, intolerance of heat or cold, lightheadedness after eating a large meal, fatigue, and exercise intolerance. The main signs of failure of the SNS are

inability to maintain blood pressure during standing (orthostatic hypotension), after a meal (post-prandial hypotension), after exercise, or during exposure to heat.

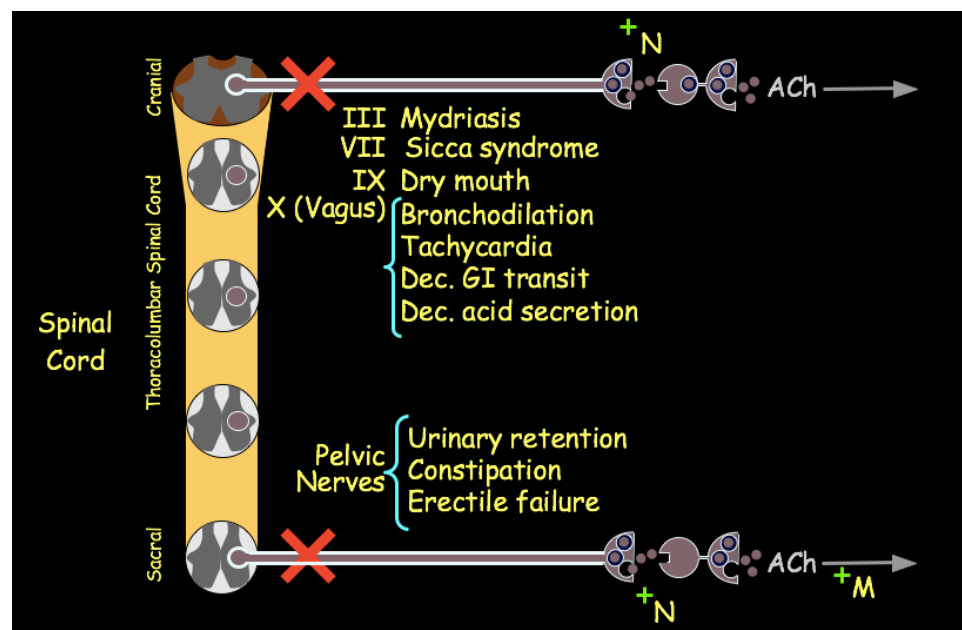
Increased activity of the sympathetic noradrenergic system (SNS) produces its effects via the release of norepinephrine, especially in the blood vessels and heart. The released norepinephrine constricts blood vessels in the skin, kidneys, gut, and skeletal muscle. Because of the constriction of blood vessels in the skin the patient may look pale.



Symptoms and signs of sympathetic noradrenergic system (SNS) overactivity or stimulation

Norepinephrine released from sympathetic nerves in the skin also causes the hair to stand up and produces goosebumps. Stimulation of the sympathetic nerves in the salivary glands increases the flow of thick saliva. Signs of increased SNS include increased blood pressure or heart rate, pallor, and trembling.

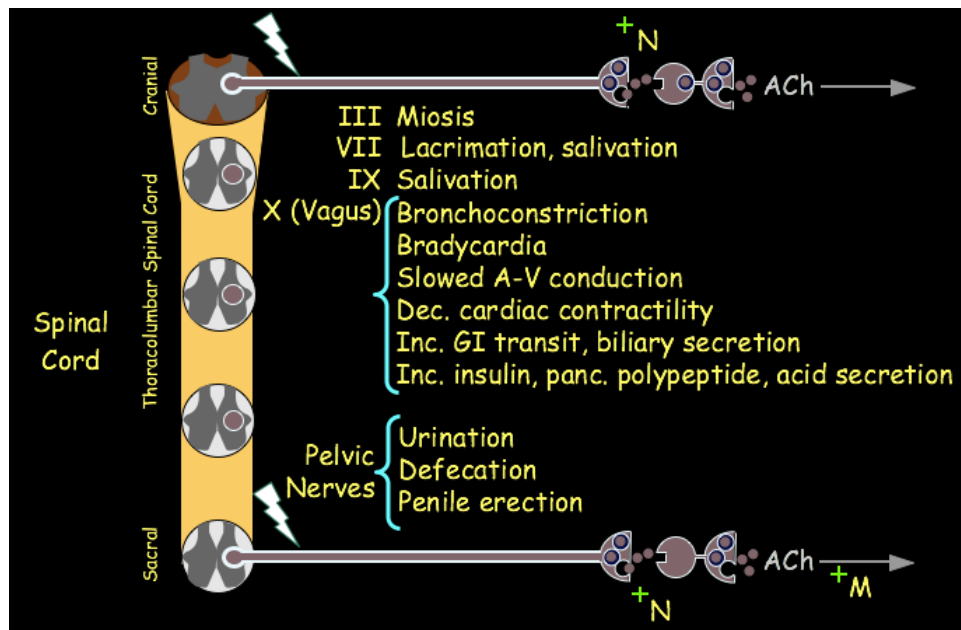
Increased activity of the parasympathetic nervous system (PNS) produces its effects via release of acetylcholine in several organs of the body. The patient notes increased gut motions, nausea, urinary urgency or frequency, increased production of watery saliva, increased tear production, and decreased visual adaptation to the dark. Signs of increased PNS activity include slow heart rate, increased bowel sounds, increased salivation and tear production, and constricted pupils.



Symptoms and signs of parasympathetic nervous system (PNS) underactivity or failure

Symptoms of PNS failure include dry mouth, dry eyes, constipation, difficulty beginning urination, and erectile failure in men. Signs of PNS failure include decreased salivation, a dry, raspy voice, decreased bowel sounds, increased heart rate, and enlargement of the urinary bladder due to urinary retention.

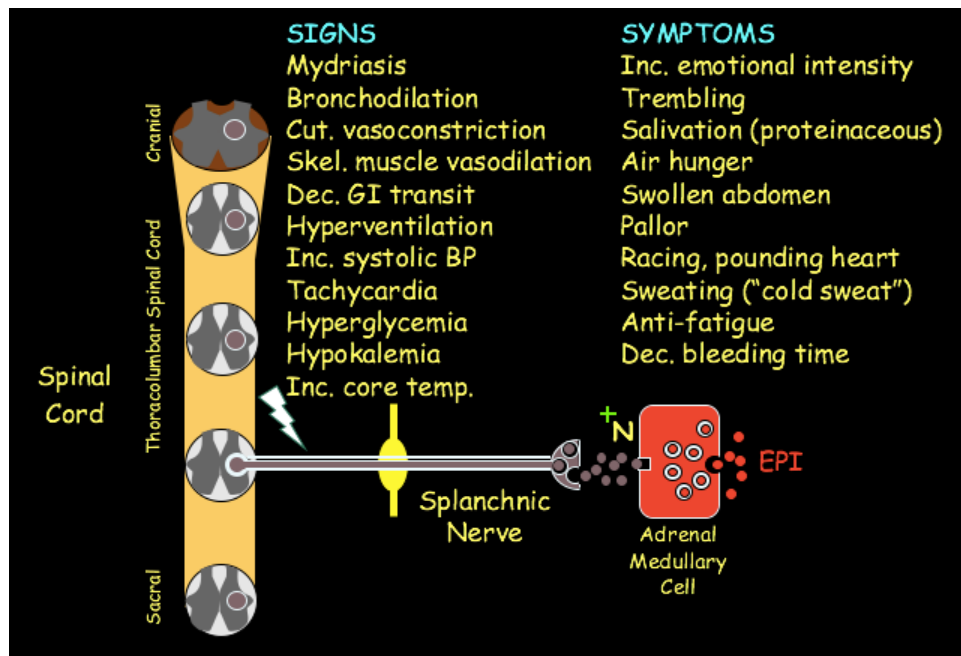
Increased activity of the sympathetic cholinergic system (SCS) produces its effects via release of acetylcholine at sweat glands. The patient reports increased sweating, during heat exposure, exercise, after eating (gustatory sweating), during emotional distress, or at rest. The main symptoms and signs of SCS failure are from decreased sweating.



Signs of parasympathetic nervous system (PNS) overactivity or stimulation

Increased activity of the sympathetic adrenergic system (SAS) produces its effects via release of adrenaline from the adrenal glands.

Symptoms of SAS activation include a sense of energy or increased emotional intensity, anxiety, a sense of the heart beating (palpitation), or an increased rate or depth of breathing.

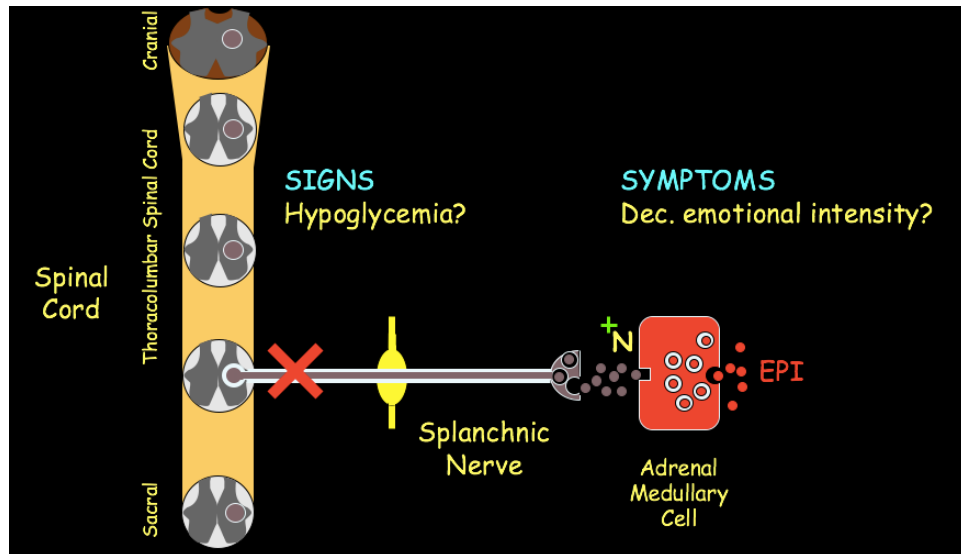


Symptoms and signs of sympathetic adrenergic system (SAS) overactivity or stimulation

Signs of SAS activation include paleness of the skin, due to constriction of local blood vessels, trembling, a tendency to decreased bleeding time due to platelet activation, sweating, and increased blood glucose levels.

It is difficult to distinguish alterations in enteric nervous system activity from alterations in parasympathetic nervous system activity in the gut.

Whether SAS failure produces symptoms or signs is unclear. Perhaps there is a tendency to hypoglycemia.

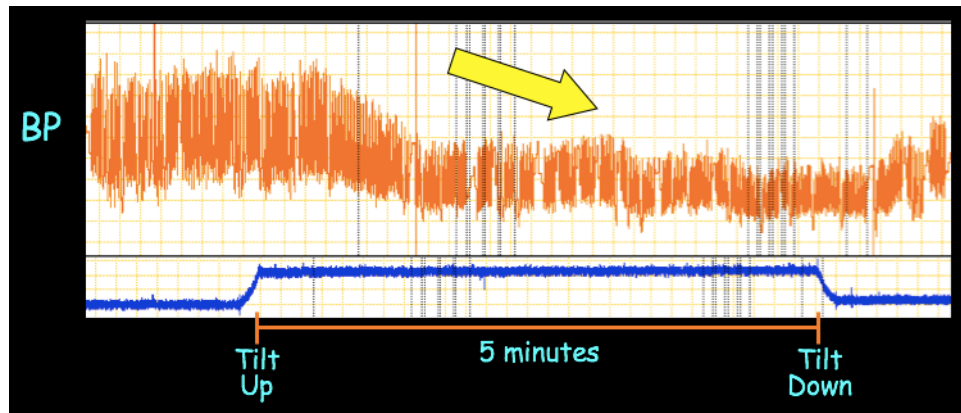


There seem to be few symptoms or signs of sympathetic adrenergic system (SAS) underactivity or inhibition.

WHAT IS ORTHOSTATIC HYPOTENSION?

Normally when you stand up you don't notice much that is different. Nevertheless, several automatic, largely unconscious, reflexive changes are required for maintaining delivery of blood to the brain in response to the seemingly simple act of standing up. When the reflexes fail, you can't tolerate standing still.

Orthostatic hypotension (OH) is a sign, something a doctor can observe or measure that provides objective evidence of a disease. Inability to tolerate standing up, or orthostatic intolerance, is a symptom, a complaint about something abnormal a person notices that provides subjective evidence of a disease.



Orthostatic hypotension: a 20 point or larger fall in blood pressure after a person has been upright for a few minutes from lying down.

Orthostatic hypotension (OH) refers to a persistent, consistent problem, not to episodes. If the systolic blood pressure persistently and consistently falls by more than 20 millimeters of mercury (mmHg) between lying flat and standing up, this is orthostatic hypotension. By consensus, experts define OH in terms of a fall in the systolic blood pressure by at least 20 mmHg or a fall in diastolic blood pressure by at least 10 mmHg between lying down and standing up for at least 3 minutes. Doctors sometimes use different definitions, but the 20 mmHg fall in systolic blood pressure seems to be a common theme in research reports. If the blood pressure while lying down is very high, then more than a 20 mmHg fall in systolic pressure may be required for the doctor to diagnose orthostatic hypotension.

The level of the blood pressure, as well as levels of all the main numbers of the body, such as your temperature, your oxygen level, and your glucose level, are kept in check by reflexes. You can think of reflexes in terms of negative feedback loops. When your blood pressure falls, such as because of injection of

a drug that relaxes blood vessels, sensors convey this information to the brain. The brain directs activation of the sympathetic noradrenergic system, which tightens the blood vessels, tending to bring the blood pressure back up.

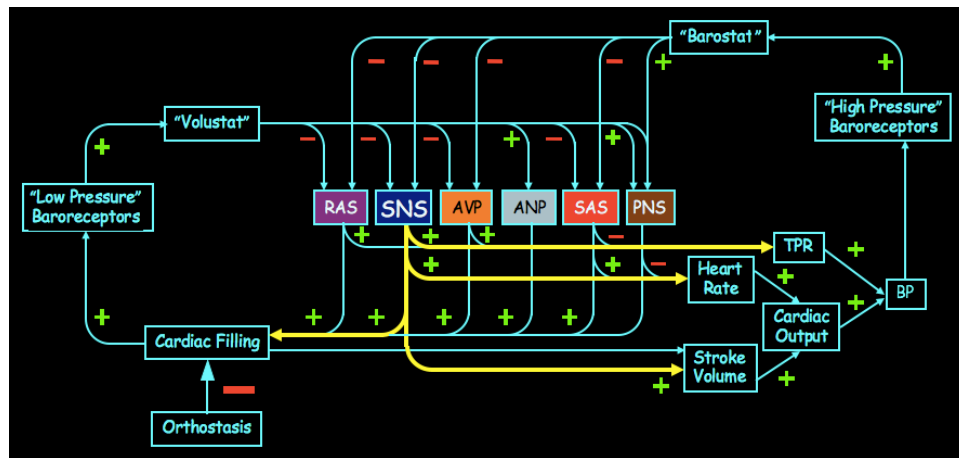
Orthostatic hypotension is a key sign of failure to tighten blood vessels reflexively by activation of the sympathetic noradrenergic system. In other words, orthostatic hypotension is a sign of sympathetic neurocirculatory failure.

A fall in blood pressure when the patient stands up or is tilted head-up on a tilt table (orthostatic hypotension) is an important sign of failure of the sympathetic noradrenergic system.

Many factors besides failure of the sympathetic noradrenergic system, however, can cause orthostatic hypotension.

Prolonged bed rest for virtually any reason can do this. Indeed, in the American space program, a study of normal volunteers found that after prolonged bed rest with the head slightly down, healthy people can have orthostatic hypotension. It should not be surprising that elderly, bedridden patients also often have orthostatic hypotension.

Orthostatic hypotension can also result from conditions that cause depletion of blood volume, such as heavy menstrual periods or gastrointestinal hemorrhage from a bleeding ulcer. Any of several drugs can do this, including tricyclics, monoamine oxidase inhibitors, and ganglion blockers.



A complex neuroendocrine network maintains blood pressure during upright posture (orthostasis). The sympathetic noradrenergic system (SNS) is the main effector system in this network.

There are many causes of orthostatic hypotension besides sympathetic noradrenergic system failure.

Doctors may have different opinions about the amount of orthostatic hypotension that is clinically significant. Normally the systolic blood pressure falls slightly during standing up, because the heart is ejecting less blood, and normally the diastolic pressure does not fall at all, because of the constriction of blood vessels in the body as a whole by way of the baroreflex and activation of the sympathetic noradrenergic system.

Some people have a fall in blood pressure accompanied by lightheadedness as soon as they get up, but then the blood pressure comes up to normal. Most experts do not consider this to be orthostatic hypotension, because the fall in blood pressure

is not sustained.

Any of several diseases can produce orthostatic hypotension from sympathetic neurocirculatory failure. These include diabetes, amyloidosis, pure autonomic failure (PAF), multiple system atrophy (MSA), Parkinson's disease (PD), and autoimmune autonomic ganglionopathy (AAG).

There are several other dysautonomias in which the patients cannot tolerate prolonged standing, even though they do not have persistent, consistent orthostatic hypotension. These disorders come under the heading of chronic orthostatic intolerance.

What is Orthostatic Intolerance?

A major way dysautonomias cause problems is by producing orthostatic intolerance.

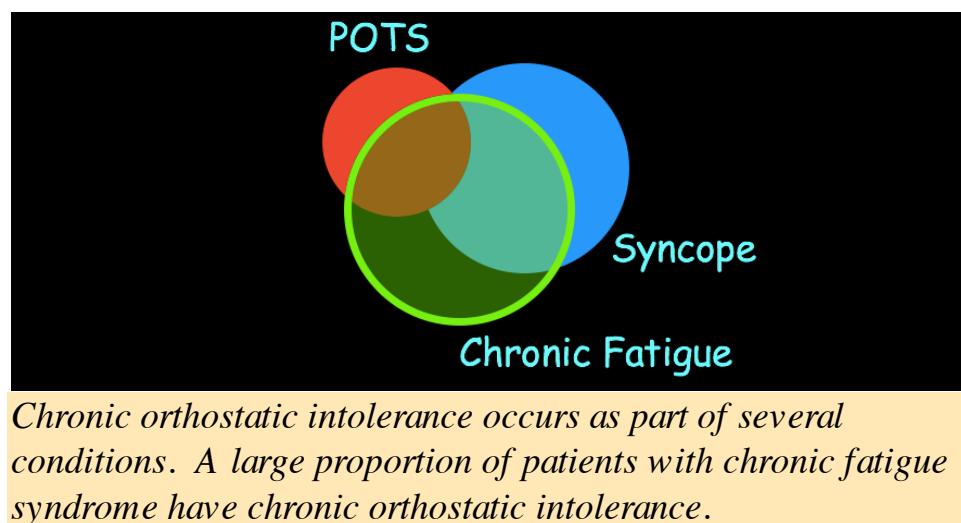
Patients with orthostatic intolerance can't tolerate prolonged standing.

Neither orthostatic intolerance nor orthostatic hypotension is a diagnosis. A diagnosis is a decision about the cause of a specific case of disease.

It is thought that about 60% of patients with chronic fatigue syndrome have chronic orthostatic intolerance, with postural tachycardia syndrome (POTS), neurocardiogenic syncope (fainting), or both. Much less commonly, chronic orthostatic intolerance can be a manifestation of arterial baroreflex failure.

Remember that orthostatic intolerance is based on symptoms, such as dizziness or lightheadedness while standing.

Orthostatic intolerance is not a sign, because it isn't something an observer can measure objectively. And it isn't a disease, although there are many diseases that produce orthostatic intolerance.



The fact that there are many possible causes of orthostatic intolerance poses a challenge to doctors trying to come up with a diagnosis to explain orthostatic intolerance in a particular patient. A starting point in identifying a cause of orthostatic intolerance is to determine whether the patient has failure of the sympathetic noradrenergic system to regulate the heart and blood vessels correctly. In dysautonomias that produce chronic SNS failure, the patient always has a fall in blood pressure during standing (orthostatic hypotension).

In other forms of chronic orthostatic intolerance, the person does not have sympathetic neurocirculatory failure, and the

blood pressure does not fall consistently when the person stands up (although the person can have delayed orthostatic hypotension after many minutes of standing). Instead, the person feels dizzy or lightheaded during standing, even though the blood pressure is maintained.

Orthostatic hypotension may or may not produce orthostatic intolerance, and orthostatic intolerance can occur without orthostatic hypotension.

In the evaluation of a patient with chronic orthostatic intolerance in which the patient does not have evidence of sympathetic neurocirculatory failure, doctors often prescribe a tilt table test. The chapter about autonomic function testing discusses the tilt table test.

Doctors often do tilt table testing in patients who cannot tolerate standing (orthostatic intolerance) and do not have a fall in blood pressure during standing (orthostatic hypotension).

In general, there are two types of positive tilt table test result. If the patient had an excessive, progressively more severe increase in heart rate during the tilting, this would be consistent with postural tachycardia syndrome, or POTS. If the patient had a sudden decrease in the level of consciousness or actually lost consciousness (syncope), this would be consistent with neurocardiogenic syncope (also called autonomically mediated syncope, reflex syncope, or fainting). Autonomically mediated syncope is virtually always associated with a fall in blood

pressure, or neurally mediated hypotension. A tilt table test can also yield results consistent with both POTS and neurocardiogenic syncope, such as when the patient has a large increase in pulse rate followed by a sudden fall in pulse rate back to normal but with neurally mediated hypotension and syncope.

Once a diagnosis of POTS is made, the workup may continue to determine if the rapid pulse is a primary problem or is part of a compensation in which activity of the sympathetic noradrenergic system outflow to the heart is increased. The section about POTS discusses this workup.

Fainting involves sudden changes in autonomic functions that, taken together, decrease blood flow to parts of the brain required for consciousness. Between episodes of fainting, patients with repeated bouts of neurocardiogenic syncope may not feel well and complain of non-specific symptoms such as fatigue, heat intolerance, headache, chronic pain, exercise intolerance, and orthostatic intolerance.

Uncommonly, orthostatic intolerance reflects failure of baroreflexes. In this situation, the sympathetic noradrenergic system is not activated appropriately in response to a decrease in blood pressure or in response to a decrease in venous return to the heart. Baroreflex failure does not consistently cause orthostatic hypotension, but it always causes large swings in blood pressure, both high and low, because of the inability to keep the blood pressure within limits. Baroreflex failure occurs in some people years after irradiation of the neck, such as for treating a cancer. The radioactivity exposure accelerates aging-

related stiffness of the carotid arteries in the neck—arteriosclerosis. Since the baroreceptors are distortion receptors, the stiffening interferes with the ability of the baroreceptors to sense changes in blood pressure.

Baroreflex failure is also a known complication of tumors and surgery for tumors in the lower brainstem, because this is the location of the “barostat” for blood pressure regulation.

Orthostatic intolerance can be associated with abnormal levels of adrenaline-like chemicals.

Measurements of plasma levels of norepinephrine and adrenaline can provide useful information in the evaluation of chronic orthostatic intolerance. In patients with chronic orthostatic intolerance from orthostatic hypotension, failure to increase plasma norepinephrine by the normal amount during standing (more than 60% by 5 minutes) can indicate failure to activate the sympathetic noradrenergic system, and an increase in plasma norepinephrine to a high level can indicate recruitment of the sympathetic noradrenergic system as part of an attempt to compensate for decreased venous return to the heart, such as from dehydration. Among patients with chronic orthostatic intolerance who do not have orthostatic hypotension, those with POTS often have high plasma norepinephrine levels when the patients are upright. Patients with neurocardiogenic syncope (fainting), with or without POTS, have high plasma adrenaline levels at the time of fainting.

TESTS FOR DYSAUTONOMIAS

There are many tests that can be used to evaluate patients with known or suspected dysautonomias. No single test assesses all the components of the autonomic nervous system simultaneously. It can be difficult to distinguish a functional problem of the nerves themselves from a central nervous system problem that alters reflexes mediated by those nerves.

Most centers that carry out autonomic function testing use more than one type of test. No center uses all the tests described in this section.

OVERVIEW OF AUTONOMIC FUNCTION TESTS

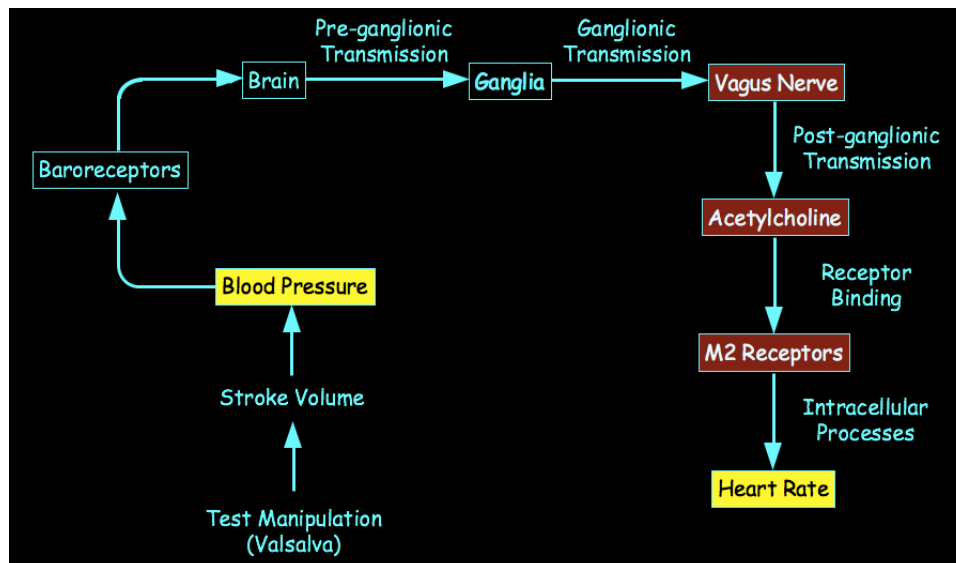
The most important autonomic function test is the medical history.

In the United States, payment by third party payers for management of patients with dysautonomias is based mainly on procedures, even though it is the autonomic history that is most important. Autonomic history-taking can't be done well in a brief clinic visit. This is a growing problem for community based physicians.

Tests for dysautonomias can be divided into physiological, neuropharmacologic, neurochemical, neuroimaging, and genetic.

Physiological tests involve measurements of a body function in response to a manipulation such as standing, tilt table-testing, or a change in room temperature.

There are always several steps between the brain's directing changes in nerve traffic in the autonomic nervous system and the physiological measures that are chosen to track the autonomic changes. Because of this indirectness, results of physiological tests can be difficult to interpret or may not identify a problem accurately.

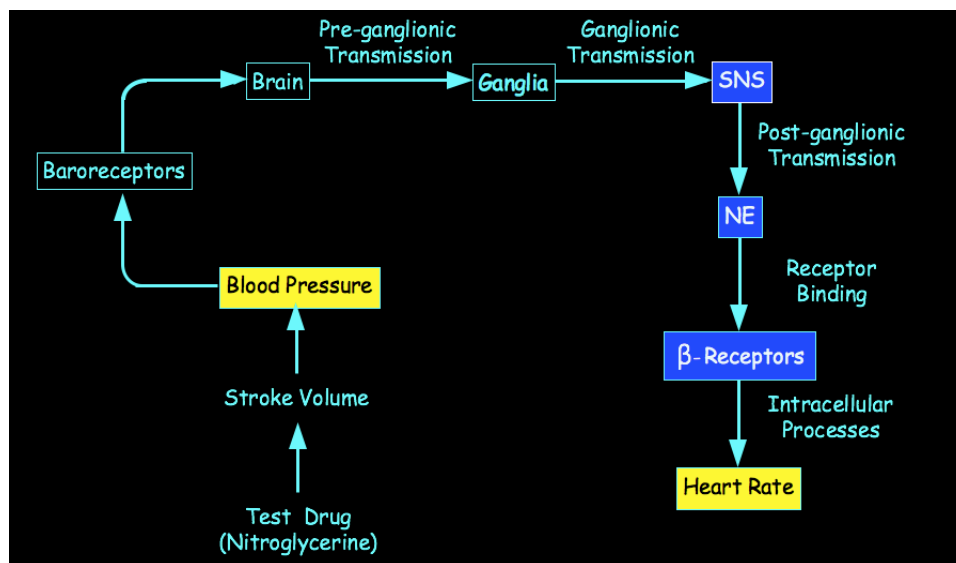


Physiological tests involve manipulation of a body function such as blood pressure and measurement of a different body function such as pulse rate.

Neuropharmacologic tests involve giving a drug and measuring its effects. Neuropharmacologic tests of the autonomic nervous system involve measuring effects of drugs a physiological measure or sometimes on levels a biochemical such as norepinephrine. There always is at least some risk of side

effects of test drugs. In addition, test drugs can interact with medications the patient is on to treat the disease or with other conditions the patient has.

Sometimes results of neuropharmacologic tests can be as difficult to interpret as those of physiologic tests. For instance, a neuropharmacologic test of the role of the sympathetic noradrenergic system in a person's high blood pressure might include measuring the effects of a drug that blocks sympathetic nerve traffic on blood pressure, because a large fall in blood pressure would suggest an important role of the sympathetic nervous system in keeping the blood pressure high. But if blocking the sympathetic nerve traffic compensatorily activated



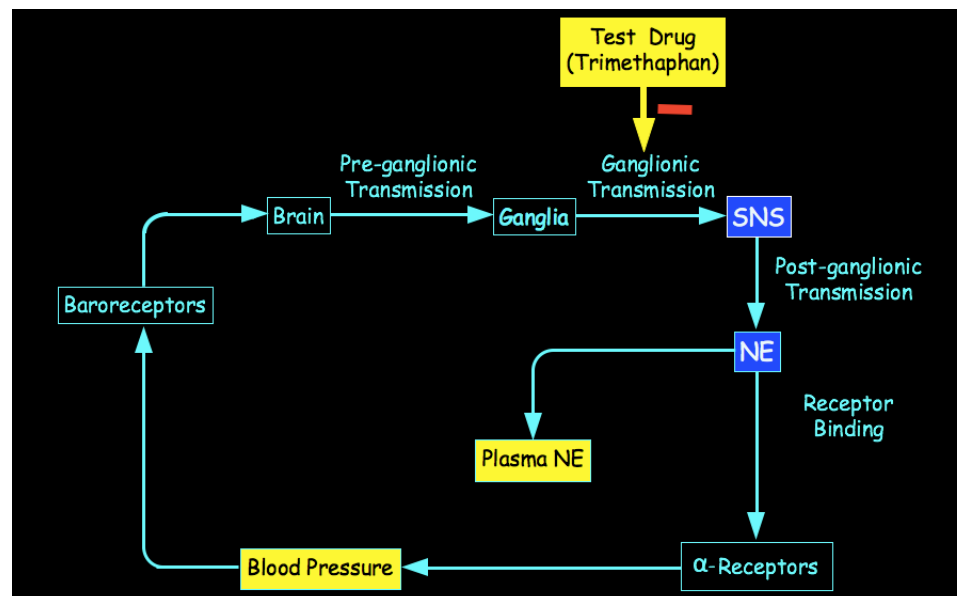
Neuropharmacologic tests involve drugs that affect the autonomic nervous system.

another system that also increased blood pressure, then the sympathetic blocking drug would not decrease the pressure, and the doctor might mistakenly think that the sympathetic

noradrenergic system wasn't involved with the patient's high blood pressure.

Neurochemical tests involve measuring levels of body chemicals, such as the catecholamines, norepinephrine and adrenaline, either under resting conditions or in response to physiological or neuropharmacologic manipulations. Several factors influence plasma norepinephrine levels, besides release from sympathetic nerves.

Neurochemical tests can be done on blood samples that are drawn while the patient is at rest lying down, during a physiological manipulation such as exercise or tilting on a tilt-table, or during a neuropharmacologic manipulation such as



Neurochemical tests involve measuring chemicals such as plasma norepinephrine that indicate functions of parts of the autonomic nervous system. Physiological and neurochemical measures can be assessed simultaneously.

blockade of sympathetic nerve traffic by a drug.

Neurochemical tests themselves are safe, but the type of body fluid sampling, such as arterial blood sampling or cerebrospinal fluid sampling after a lumbar puncture, can involve some risk.

The results can be affected importantly by dietary constituents, drugs, or dietary supplements the patient is taking and by the exact conditions at the time of sampling. Relatively few centers have a clinical neurochemistry laboratory to carry out the assays.

There is no chemical test of parasympathetic nervous system activity. This is because acetylcholine, the chemical messenger of the parasympathetic nervous system, is broken down by an enzyme almost as soon as acetylcholine enters body fluids such as the plasma.

Neurochemical testing to examine activity of the sympathetic noradrenergic system based on plasma norepinephrine levels can be difficult to interpret. Plasma norepinephrine levels are determined not only by the rate of entry of norepinephrine into the plasma but also by the rate of removal (clearance) of norepinephrine from the plasma. In addition, plasma norepinephrine levels are determined by a variety of processes that take place within the sympathetic nerves.

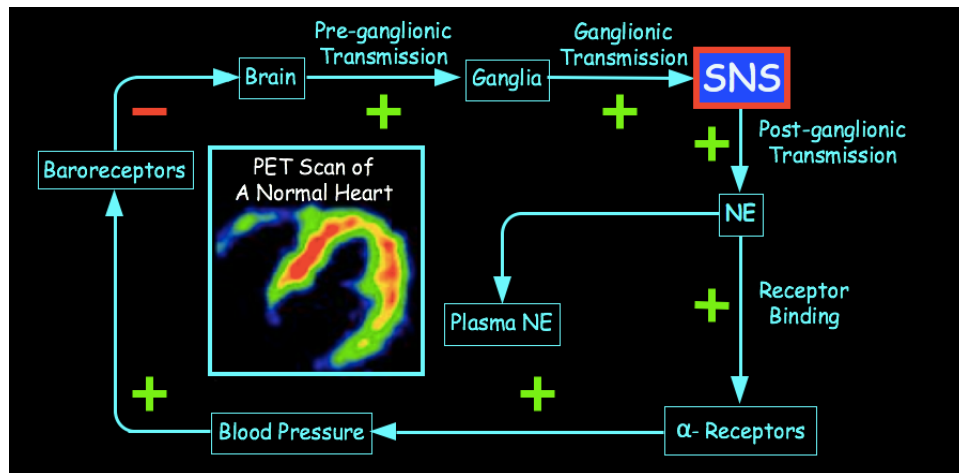
Neurochemical testing by plasma norepinephrine levels requires a carefully controlled testing situation and expert technical analysis and interpretation. Few clinical laboratories measure plasma levels of catecholamines such as norepinephrine and adrenaline, from the point of view of diagnosis or management

of dysautonomias, and laboratories vary in the validity of the assay methods they use.

Some blood tests involve measuring levels not of neurochemicals but of factors in the circulation that affect the functioning of one or more components of the autonomic nervous system. For instance, there is an uncommon form of dysautonomia in which there is a high titer of an antibody to the nicotinic cholinergic receptor that is required for relaying signals in the ganglia. The associated conditions have been called autoimmune autonomic neuropathy or autoimmune autonomic ganglionopathy.

Neuroimaging tests, which are relatively new, involve actually visualizing the autonomic nerve supply in body organs. Central nervous system neuroimaging can also be used to identify brain diseases that are associated with dysautonomias. For instance, different types of scans can identify the loss of nerve terminals that contain dopamine in the brain in Parkinson's disease or identify abnormalities of brain structures that regulate the autonomic nervous system.

Sympathetic neuroimaging is done in few centers, and although this type of testing can produce striking images of the sympathetic innervation of the heart, this provides mainly anatomic information about whether sympathetic nerves are present. It is much more difficult to determine from sympathetic neuroimaging whether the nerves are functioning normally or not.



Neuroimaging tests involve seeing parts of the nervous system, such as sympathetic nerves supplying the heart in PET scans.

As yet there is no generally accepted neuroimaging test to visualize parasympathetic nerves.

Examining nerves in skin biopsy specimens by immunofluorescence microscopy can be considered to be another sort of neuroimaging.

Genetic tests involve analyses of genetic material (DNA) for abnormalities of specific genes that produce or predispose to the development of particular diseases.

Genetic tests involve some ethical issues, such as patient confidentiality and whether an individual wishes to know the test result, if there is no way to prevent the disease.

Researchers may be reluctant to provide results of genetic tests, if the laboratory is not certified to do diagnostic testing.

Now we will go over in more detail the different forms of

clinical testing of the autonomic nervous system.

The Most Important Test of All

The most important test in the evaluation of dysautonomia is the medical history.

Symptoms are feelings that the patient reports to the doctor as part of the medical history. Signs are medical findings that a doctor detects during a physical examination.

The medical history consists of several parts. These include the Chief Complaint, the History of the Present Illness (HPI), the Past History, the Family History, the Personal and Social History, and the Review of Systems (ROS). Each of these parts is important for diagnosing and managing dysautonomias, but the key component is the HPI.

The Chief Complaint is a single phrase or sentence that describes in the patient's own words what has been bothering the patient that has led the patient to come in for evaluation. The Chief Complaint can be surprisingly informative. For example, I once evaluated a local elderly woman who was referred for pure autonomic failure, because she had persistent, consistent orthostatic hypotension. I asked her, "We'll be going into detail about your medical history, but for now, in a single phrase or sentence, can you tell me what it is that's been bothering you that's brought you here today?" I was expecting she would report dizziness or lightheadedness when she was upright, or perhaps fainting episodes while standing on line at a checkout counter. Instead, her Chief Complaint was that she couldn't make spit and she was constipated.

Dry mouth and constipation are symptoms of parasympathetic nervous system failure, not sympathetic noradrenergic system failure. I asked if she sweated like other people, and she said no, because she couldn't sweat at all. Sweating is a sympathetic cholinergic function. In other words, she had symptoms of a pandysautonomia, involving all the components of the autonomic nervous system. Eventually she was found not to have pure autonomic failure but to have a previously undescribed condition, autoimmune autonomic ganglionopathy from a circulating antibody to the neuronal nicotinic receptor. The first clue to the diagnosis was her unexpected Chief Complaint.

The History of the Present Illness (HPI) is a narrative history of the condition. It is best to obtain the HPI from the patient directly. There are records to review of hospitalizations, test results, and previous accounts of the medical history and physical examination; however, these are subject to mistakes and often are uninformative. On the other hand, the patient's own story of the chronology of his or her symptoms, especially with the help of family or significant others, is likely to be both correct and informative. Unfortunately, this key aspect of the medical encounter is not reimbursed adequately considering its importance and the time and effort involved.

I take what the patient says as gospel. The patient knows best how he or she feels, and in my experience patients always tell the truth.

Obtaining the medical history, especially the HPI, is a skill that must be honed by learning and experience, ideally under the direct supervision of a mentor.

A complete listing of all prescribed medications, over-the-counter medications, herbal remedies, and dietary supplements is a key part of the medical history, not only because these can affect autonomic function but also because they can interact to produce unexpected, serious adverse events.

Chief Complaint: In a few words, what's the main problem bothering you that brings you here today?

HPI: When was the last time you felt completely healthy?

What was the first thing that went wrong?

What happened next?

Have you noticed anything that makes the problem worse or better?

What treatments have been tried, and how did you respond?

Autonomic Review of Systems:

Who does your shopping? Are you able to tolerate standing, exercise, heat, a large meal?

Do you sweat like other people?

Do you make spit like other people?

Have you noticed any problems with urination?

Have you noticed any problems with bowel movements?

Have you noticed any problems with sexual function?

Some aspects of the screening autonomic history

For example, I had a patient with multiple system atrophy (MSA) who first came to medical attention because of paroxysmal high blood pressure after taking *ma huang* tea. He had thought this would alleviate his sense of fatigue and lack of energy. The active ingredient in *ma huang* tea is ephedrine, an amphetamine. The drug increased delivery of norepinephrine to its receptors, which caused the blood pressure to increase, and because of arterial baroreflex failure as part of the patient's disease the increase in blood pressure was not buffered by the baroreflex. The patient developed a severe headache and went to the emergency room. Because of his headache and

paroxysmal hypertension the physicians thought at first that he had a stroke from subarachnoid hemorrhage.

Ma huang is no longer sold as a dietary supplement in the US, but yohimbe bark is. Yohimbine, a drug derived from yohimbe bark, increases norepinephrine release. In a patient with baroreflex failure, taking this dietary supplement could result in severe hypertension, in a manner analogous to my MSA patient.

TIMING IS EVERYTHING

In obtaining the history of the present illness (HPI), one of the most important skills a clinician can acquire is the ability to get the sequence straight.

I usually start by asking the patient, “When was the last time you felt completely well?” The answers can range from “I’ve always been sick,” to “I was fine until...” a particular date, to “It was such a gradual thing, I don’t know.”

Some dysautonomias develop in a rather stereotyped sequence. An example is the cerebellar form of multiple system atrophy (MSA-C) in a man. Men with MSA-C typically relate that the first thing to go wrong, in retrospect, was erectile failure. In my opinion, in a man with central neurodegeneration and orthostatic hypotension, the absence of erectile failure as an early finding rules out MSA-C. The erectile failure is followed by urinary problems—especially urinary retention, eventually to the point of requiring self-catheterization. Then come slurred speech, a wide-based, unsteady gait “like a drunken sailor,” and lightheadedness when standing.

In obtaining the details about symptoms of dysautonomias, it is also important to determine which situations make things worse and which make them better. For instance, patients with neurogenic orthostatic hypotension often relate that their symptoms are worst in the morning, upon heat exposure, after eating a large meal, or after exercise.

Because of associations of autonomic failure with non-motor aspects of Lewy body diseases in Parkinson's disease and pure autonomic failure, it is important to ask about whether the patient is able to smell things like other people do, whether the patient sees things like other people do, and whether the patient has any problems with sleep. The clinician is looking for evidence of olfactory dysfunction, visual hallucinations (a feature of dementia with Lewy bodies), and dream enactment behavior.

In patients with possible postural tachycardia syndrome (POTS) it is valuable to ask about whether the patient has "double-jointedness" or stretchy skin, since these can be clues to the existence of Ehlers-Danlos syndrome. Later on you will learn about the "coat hanger sign" and the "water bottle sign" in dysautonomias like POTS. Again, the sequence of events can be very informative. Subacute development of orthostatic intolerance after a viral illness suggests an autoimmune component of the pathophysiology, whereas a history of frequent fainting or "seizures" since childhood points more to a congenital, genetic component. In the evaluation of a patient with POTS, which occurs mainly in relatively young women, it is important to ask, in a private setting, about emotional, physical, or sexual abuse in childhood. These can have long-term consequences in terms of chronic fatigue, altered memory

or concentration, and panic or anxiety.

In a patient with labile blood pressure and orthostatic intolerance, a remote history of irradiation of the neck brings up the possibility of arterial baroreflex failure due to accelerated arteriosclerosis in the carotid sinus area.

SYMPTOMS & SIGNS OF DYSAUTONOMIAS: ANOTHER LOOK

Altered functions of each of the components of the autonomic nervous system result in particular symptoms and signs.

Failure of the sympathetic noradrenergic system (SNS) manifests as orthostatic hypotension, meaning a persistent, consistent fall in blood pressure each time the patient stands up. Orthostatic hypotension can produce symptoms such as lightheadedness, dizziness, faintness, visual changes, and muscle weakness. Collectively these symptoms are termed “orthostatic intolerance.” Orthostatic hypotension can also occur without producing symptoms.

Orthostatic hypotension is a cardinal sign of SNS failure.

Orthostatic hypotension often is accompanied by post-prandial lightheadedness and hypotension. “Post-prandial” means after eating a meal. In patients with SNS failure, heat exposure also

Sympathetic Noradrenergic System (SNS) Failure

Orthostatic intolerance & hypotension

Post-prandial lightheadedness & hypotension

Heat intolerance & hypotension

Fatigue

Tendency to slow pulse rate during exercise

"Coat hanger" pain

Droopy eyelids (ptosis)

Decreased ability to ejaculate

Tendency to constricted pupils

No goosebumps

Symptoms and signs of SNS failure

can decrease the blood pressure.

Orthostatic hypotension is a fundamental sign of SNS failure.

SNS hyperactivity produces pallor, due to constriction of blood vessels in the skin. Blood pressure tends to increase, along with the heart rate. The heart may pound (palpitation). The hair may bristle, due to activation of noradrenergic nerves supplying *arrector pili* (pilomotor) muscles. The pupils may be dilated, and there may be increased salivation.

Parasympathetic nervous system (PNS) failure produces a variety of symptoms. Probably the most prominent are dry mouth and constipation. Other manifestations include a

Sympathetic Noradrenergic System (SNS) Hyperactivity

Pallor

Tendency to high blood pressure

Tendency to fast pulse rate

Trembling

Bristling hair (piloerection)

Sweating

Increased production of thick saliva

Tendency to dilated pupils (mydriasis)

Symptoms and signs of SNS hyperactivity

tendency to urinary retention, slowed gastrointestinal transit, and erectile failure in men.

Parasympathetic Nervous System (PNS) Failure

Dry mouth (decreased watery saliva)

Constipation

Dry eyes

Urinary retention

Tendency to fast pulse rate with low variability

Slow gastrointestinal transit

Erectile failure

Symptoms and signs of PNS failure

PNS hyperactivity results in increased salivation, a tendency to

slow pulse rate, nausea, gastrointestinal upset, and urinary frequency or urgency.

The main symptoms of parasympathetic nervous system (PNS) failure are dry mouth and constipation.

The sympathetic cholinergic system (SCS) is the main part of the autonomic nervous system mediating sweating. SCS failure manifests as decreased sweating.

Parasympathetic Nervous System (PNS) Hyperactivity

- Increased salivation
- Tendency to slow pulse rate or heart block
- Nausea & vomiting
- Diarrhea or fast gastrointestinal transit
- Tendency to constricted pupils (miosis)
- Urge to urinate (increased bladder motility)
- Increased stomach acid secretion

Symptoms and signs of PNS hyperactivity

Adrenaline, the main chemical messenger of the sympathetic adrenergic system (SAS), is a hormone, and as such adrenaline is distributed by the bloodstream to all the organs (with the exception of most of the central nervous system). Adrenaline injection produces characteristic symptoms, including pallor, increased sweating, cardiovascular stimulation, dilated pupils, and increased blood glucose levels. Adrenaline exerts well-known anti-fatigue effects and tends to increase the intensity of emotional experiences. SAS failure, on the other hand,

Sympathetic Cholinergic System (SCS) Failure

Decreased sweating

Sympathetic Cholinergic System (SCS) Hyperactivity

Increased sweating

Altered SCS function involves changes in sweating.

produces relatively few symptoms or signs—perhaps a tendency to fatigue or to hypoglycemia.

SAS hyperactivity produces many symptoms and signs, such as pale skin, increased sweating, a forceful heartbeat, and dilated pupils.

Sympathetic Adrenergic System (SAS) Hyperactivity

Pallor

Increased sweating

Increased heart rate & contractility

Increased systolic & pulse pressures

Dilated pupils (mydriasis)

Increased blood glucose (hyperglycemia)

Decreased gastrointestinal transit (functional ileus)

Tendency to increased emotional intensity, anti-fatigue

Tendency to decreased serum potassium (hypokalemia)

Tendency to decreased bleeding time

Tendency to increased core temperature

Some symptoms and signs of SAS hyperactivity

COMPOSITE AUTONOMIC SYMPTOM SCORE (COMPASS)

Over the years, progressively more refined “composite” autonomic symptom scores (COMPASS) have been introduced. The “COMPASS 31” scale contains a total of 31 questions in 6 domains, yielding an overall autonomic symptom score from 0 to 100. The domains are orthostatic intolerance (4 questions), vasomotor (3 questions), secretomotor (4 questions), pupillomotor (5 questions), bladder (3 questions), and gastrointestinal (including diarrhea, constipation, and gastroparesis, 12 questions). Erectile dysfunction is not included, since this is gender specific. For each question there is a numeric rating based on factors such as site, consistency, severity, frequency, or trends.

Here are the topics and simplified questions of the COMPASS 31:

1. Orthostatic intolerance: In the past year, have you ever felt faint, dizzy, “goofy”, or had difficulty thinking soon after standing up from a sitting or lying position? If so, how frequently? How severe are these feelings or symptoms? Have they changed?
2. Vasomotor: In the past year, have you ever noticed color changes in your skin, such as red, white, or purple? If so, which body parts are affected? Have these symptoms changed?
3. Secretomotor: In the past 5 years, what changes, if any, have occurred in your general body sweating? Do your eyes feel

excessively dry? Does your mouth feel excessively dry? For the symptom of dry eyes or dry mouth that you have had for the longest period of time, has this symptom changed over time?

4. Gastrointestinal: In the past year, have you noticed any changes in how quickly you get full when eating a meal? Have you felt excessively full or persistently full (bloated feeling) after a meal? Vomited after a meal? Had cramping or colicky abdominal pain? Bouts of diarrhea? If so, how frequently? How severe are the episodes? Have they changed? In the past year, have you been constipated? If so, how frequently? How severe are the episodes? Have they changed?

5. Bladder: In the past year, have you ever lost control of your bladder function? If so, how frequently? Have you had trouble completely emptying your bladder? If so, how frequently?

6. Pupillomotor: In the past year, without sunglasses or tinted glasses, has bright light bothered your eyes? If so, how frequently? How severe is this sensitivity to bright light? Have you had trouble focusing your eyes? How frequent is the problem? How severe is the problem? Is the problem with light sensitivity or focusing changing?

While internally consistent statistically and useful for research purposes, composite scoring of autonomic symptoms is inadequate from the point of view of the diagnostic interview as applied to dysautonomias. For instance, within the “orthostatic intolerance” domain, time of day, relationships with meals, exercise, and heat exposure, associated symptoms such as the coat hanger phenomenon, chronic fatigue, chronic pain, and “brain” fog all should be considered. Within the “bladder”

domain, a report of urinary retention and the need for self-catheterization is important for differentiating the parkinsonian form of multiple system atrophy (MSA-P) from Parkinson's disease with orthostatic hypotension (PD+OH). Urinary retention strongly favors MSA-P over PD+OH. The lack of inclusion of erectile dysfunction in men is rather glaring.

The COMPASS approach does not take into account the syndromic nature of particular forms of dysautonomia. For instance, in an elderly patient with parkinsonism, it is highly relevant to ask about olfactory dysfunction, since anosmia (lack of sense of smell) is common in PD+OH; about cognitive function, since dementia is more commonly associated with PD+OH than with MSA-P; about speech, since slurred speech favors MSA-P over PD+OH; and about breathing, since stridor favors MSA-P over PD+OH. In a young woman with orthostatic intolerance, asking about double-jointedness and stretchy skin may reveal Ehlers-Danlos syndrome. In a patient with labile hypertension, the past history may disclose a remote history of neck irradiation, raising the possibility of arterial baroreflex failure from carotid arteriosclerosis.

Perhaps most importantly, the COMPASS approach does not take into account the sequence of symptoms, the chronology that is the essence of the history of the present illness (HPI). For instance, in a man with central neurodegeneration, the lack of early erectile function excludes MSA. The checklist concerns only events within the past year (except for 5 years for secretomotor). In contrast, the non-directed approach to the HPI starts with a question like, "What was the first thing you noticed that went wrong?"

My screening questions generally query each of the components of the autonomic nervous system. The questions are designed not to be leading. For instance, about sympathetic cholinergic function, I ask, “Do you sweat like other people?” About sympathetic noradrenergic function, I ask, “Do you have any issues standing still?” About parasympathetic cholinergic function, I ask, “Are you able to make spit and tears like other people?” Have you noticed anything different about how your GI system is working? Have you noticed anything different about your urination? In a man I ask, “Are you able to have an erection and ejaculate?”

A PAIN IN THE NECK

In patients with orthostatic intolerance or orthostatic hypotension, standing upright can result in an annoying pain in the back of the neck and along the shoulders.



The “coat hanger phenomenon” refers to pain in the back of the neck during standing.

Because of the distribution of the discomfort, this is sometimes referred to as the coat hanger sign or coat hanger phenomenon.

The mechanism of the coat hanger phenomenon is poorly understood. I think of it as a kind of cramp, when the anti-gravity muscles holding up the head receive too little blood flow. These muscles are active all the time, which means that they are continuously using up the oxygen that is delivered to them via the arterial blood. If the blood flow falls to below a certain rate, then metabolic waste products that cause pain can build up.

WHO DOES YOUR SHOPPING?

Most patients with orthostatic intolerance are women. At the risk of seeming chauvinistic, a screening question for a woman referred for orthostatic intolerance is, “Who does your shopping?”

If the answer is, “I do. I love to shop,” then that is the end of the line of questioning. A positive answer is something like, “Well not me.” When I ask, “Why not?” the answer I’m looking for is, “Because I can’t tolerate standing still in line. I start to feel faint or lightheaded or weak, or I have to twist my legs like a pretzel, or I have to sit down.”

PRETZEL LEGS AND THE WATER BOTTLE SIGN

I remember well the first patient I evaluated with pure

autonomic failure (PAF), a rare disease manifesting with orthostatic hypotension due to loss of sympathetic noradrenergic nerves. She was sitting in a chair in the examining room with her legs twisted around each other like a pretzel.

She had learned from experience that doing this delayed the onset of feeling lightheaded when she was sitting up. By working the muscles of the legs against each other and tightening her buttocks she was squeezing blood upward in her body toward the heart.



Twisting the legs around each other like a pretzel is a sign of orthostatic intolerance.

When there is deficient reflexive sympathetically-mediated vasoconstriction during orthostasis, “pretzel legs” help maintain venous return to the heart. Adopting the same posture is a countermeasure in patients with autonomically mediated presyncope.

It is common for a patient with orthostatic intolerance to bring a

bottle of water to the clinical encounter and sip from it periodically as the history is taken. I call this the “water bottle sign.” The patients often report that although frequently drinking water doesn’t eliminate the symptoms, not drinking water rapidly makes them worse.

To me this could be a clue as to the pathophysiology of chronic orthostatic intolerance. Perhaps the kidneys are less efficient in reabsorbing filtered water, and the water bottle sign is part of a behavioral compensation. The kidneys filter about 100 mL of plasma per minute. Since there are 1440 minutes in a day, this means the kidneys filter about 144 liters per day. Since normal urine output is about 1.5 liters per day, the kidneys are roughly 99% efficient in reabsorbing water. One might expect that even the slightest decrease in efficiency would result in a tendency to dehydration.

It happens that kidney cells possess water channels called aquaporins. A classmate of mine in medical school, Peter Agre, discovered aquaporins, and for this he received a Nobel Prize in Chemistry. It might be worth looking into whether there is a problem with aquaporins in patients with chronic orthostatic intolerance who have the water bottle sign.

A BIT OF A STRETCH

Joint hypermobility (“double jointedness”) seems to occur rather frequently among patients with postural tachycardia syndrome (POTS). When obtaining the medical history in a patient with chronic orthostatic intolerance, it is worthwhile to ask whether the patient is double jointed and if so to ask what

sorts of things the patient can do that other people cannot.

Ehlers-Danlos syndrome (EDS) is an inherited connective tissue disease in which the patients have joint hypermobility, lax skin, a tendency to joint dislocation or subluxation, musculoskeletal pain, and easy bruising. EDS patients often have “Marfanoid” appearance, in that they are tall, thin, have long arms and legs, and have long thin fingers (arachnodactyly, or “spider fingers”).

POTS occurs frequently in EDS. One possible explanation for this association is that a problem with collagen in blood vessel walls makes them more stretchy or compliant, so that blood



Two components of the 9-point Beighton score

tends to pool in the abdomen or pelvis during prolonged standing.

The Beighton score is used to gauge the severity of joint hypermobility, based on 5 tests. The Beighton score is calculated as follows:

1. One point for each little finger that you can bend backwards

by more than 90 degrees.

2. One point for each thumb that you can touch to your forearm when bent backwards.
3. One point for each elbow that you can bend backwards.
4. One point for each knee that you can bend backwards.
5. One point if while standing you can bend forward and place your palms on the ground with your legs straight.

Physiological Tests

ORTHOSTATIC VITAL SIGNS

Measuring the blood pressure during supine rest and after standing up is required to detect orthostatic hypotension (OH), which in turn is a key manifestation of failure of the sympathetic noradrenergic system.

At first glance it would seem that detecting orthostatic hypotension is a simple matter. But there are issues.

According to a consensus of autonomics experts, orthostatic hypotension is “a sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 min of standing or head-up tilt to at least 60° on a tilt table.”

The consensus definition seems straightforward. There are some aspects, however, that bear comment. Briefly, the consensus definition involves compromises due to different practices among autonomics centers.

(1) What is a “sustained reduction...within 3 minutes”? How can a decrease in pressure be “sustained” if the duration of observation is less than 3 minutes?

What the experts have in mind by “sustained reduction...within 3 minutes” is that in many apparently healthy people blood pressure falls rapidly but transiently as soon as they stand up

from lying down. On the other hand, patients with neurogenic OH can have such a rapid, severe fall in blood pressure that it is unsafe to keep the patient upright for a long period of time. The consensus definition is a compromise that leaves open the possibility that a rapid fall in blood pressure may be a positive finding if the pressure doesn't return toward normal within 3 minutes.

Frankly, I avoid trying to detect OH by brachial automated cuff measurements, because they take too long. I don't want to put patients who have rapid, severe OH at increased risk of decreased blood flow to the brain if I can avoid doing so. To detect OH efficiently and safely, I use continuous (beat-to-beat) blood pressure recording via a finger cuff device.

(2) The definition doesn't mention the posture before the person stands up or is tilted, nor the time the person should be at that posture before the person stands up or is tilted.

This also is a compromise, because autonomics centers differ in their methods of obtaining orthostatic vital signs. It seems intuitively obvious that in patients with failure of the sympathetic noradrenergic system the extent of fall in blood pressure between lying down and standing is greater than the fall between being sitting and standing.

In my opinion, before the baseline blood pressure is measured, the patient should be supine (with head on pillow) for at least 10 minutes. During this time, the observer can list all the medications and dietary supplements that the patient has taken within the past 24 hours and when they were taken. The location of the measurement, the time of day, and when and

what the patient last ate should be noted (the latter because of the possibility of post-prandial hypotension).

(3) The use of “or” in “reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg” seems ambiguous. Must there be both findings, or is one sufficient?

This is another compromise. In a healthy person, diastolic pressure typically increases during orthostasis and doesn’t fall at all. Several research reports have relied only on the orthostatic fall in systolic pressure. The “or” in “reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg” allows OH to be identified even if the fall in diastolic pressure is less than 10 mmHg.

(4) How can “standing or head-up tilt to at least 60°” yield comparable results? In a patient with OH, wouldn’t head-up tilt to 90° evoke a greater fall in blood pressure than tilt to 60°? And is standing equivalent to being tilted on a tilt table?

This is yet another compromise. Many practitioners don’t have access to a tilt table. Among those who do, some tilt the patient to a full head-up position—i.e., the patient is standing upright—and others tilt the patient to 60° or another angle less than 90°. Tilting to 60° or 70° makes sense for provocative tilt table testing, since interfering with muscle pumping might increase the likelihood of a positive result (excessive orthostatic tachycardia, neurally mediated hypotension, or syncope). I don’t understand the rationale, though, of tilting to less than 90° in the evaluation of possible OH.

In order to avoid gravitational effects when the brachial cuff is below heart level, the patient's arm should be supported at heart level when the patient is upright. The patient should not have the arm extended without support, because this introduces the possibility of effects of isometric exercise on the measurement.

If you don't have access to a device for measuring blood pressure continuously and check orthostatic vital signs with an automated brachial cuff device, here's a checklist you may want to use.

Name of Test: Orthostatic Vital Signs

Patient ID:

Age/Gender:

Date:

Location of Test:

Recording Personnel:

Medications and When Last Taken:

Dietary Supplements and When Last Taken:

Content of Most Recent Meal and When Eaten:

Patient supine at least 10 minutes?

Supine BP (in mmHg) and Time of Day:

Concurrent Supine HR (in bpm):

Time of Day When Posture Changed to Standing Up:

Arm supported passively with brachial cuff at heart level?

Upright BP at 1 minute:

Upright BP (in mmHg) and Time of Day:

Concurrent Upright HR (in bpm)

Upright BP at 2 minutes:

Upright BP (in mmHg) and Time of Day:

Concurrent Upright HR (in bpm)

Upright BP at 3 minutes:

Upright BP (in mmHg) and Time of Day:

Concurrent Upright HR (in bpm)

Upright BP at 4 minutes:

Upright BP (in mmHg) and Time of Day:

Concurrent Upright HR (in bpm)

Upright BP at 5 minutes:

Upright BP (in mmHg) and Time of Day:

Concurrent Upright HR (in bpm)

If a patient with suspected OH doesn't meet the criterion fall in systolic blood pressure by 5 minutes, then in my book the patient doesn't have OH.

Heart rate usually is measured simultaneously with blood pressure. Patients with baroreflex-cardiovagal failure have a small orthostatic increment in heart rate for a given fall in blood pressure; however, such patients still have some increase in heart rate. The occurrence of an increase in heart rate during standing should not be taken as evidence against neurogenic OH.

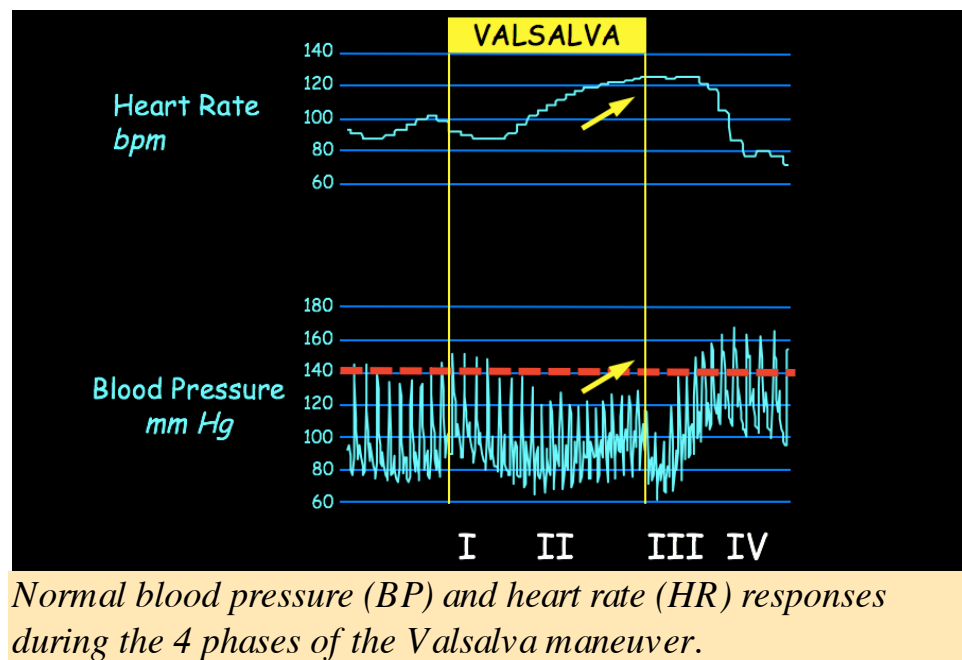
THE VALSALVA MANEUVER

Despite its apparent simplicity, the Valsalva maneuver test is one of the most important clinical physiological tests for autonomic failure. The test is done using a method to measure blood pressure continuously (beat-to-beat).

In the Valsalva maneuver, the patient blows against a resistance for several seconds and then relaxes.

The maneuver consists of blowing against a resistance for several seconds and then relaxing. Often the patient is asked to blow into a tube connected to a blood pressure gauge, moving the gauge's needle to a particular pressure (30-40 mmHg) and keeping the needle there for 10-15 seconds.

In Phase I, just after starting to squeeze, the blood is forced out of the chest, and the blood pressure increases briefly. This is mechanical and has nothing to do with reflexes.

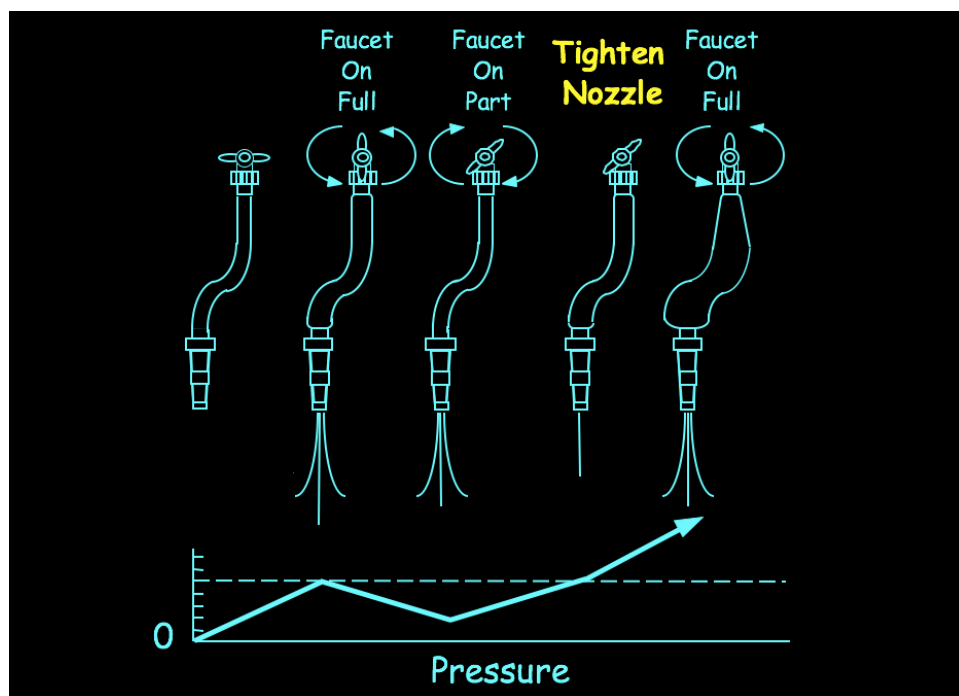


As you continue to strain, the high pressure in the chest and abdomen results in less blood reaching the heart, and the heart pumps less blood, so normally in Phase II the blood pressure

falls.

The brain picks up on this immediately and directs a reflex to occur in which outflows in the sympathetic noradrenergic system (SNS) increase, norepinephrine, the chemical messenger of the SNS, is released, the norepinephrine binds to its receptors in the blood vessel walls, and the blood vessels tighten. At the end of Phase II blood pressure therefore increases, even though the heart is still pumping out less blood.

To understand this reflex better, think of the water pressure in a garden hose.



The garden hose analogy helps understand reflexive regulation of blood pressure associated with the Valsalva maneuver.

Turning down the faucet decreases the pressure in the hose, but

you can bring the pressure back up by tightening the nozzle. The brain uses the sympathetic noradrenergic system to tighten the vascular nozzle, and so the blood pressure increases at the end of Phase II.

Also during Phase II the heart rate normally goes up, due to withdrawal of parasympathetic nervous system outflow to the heart via the vagus nerve.

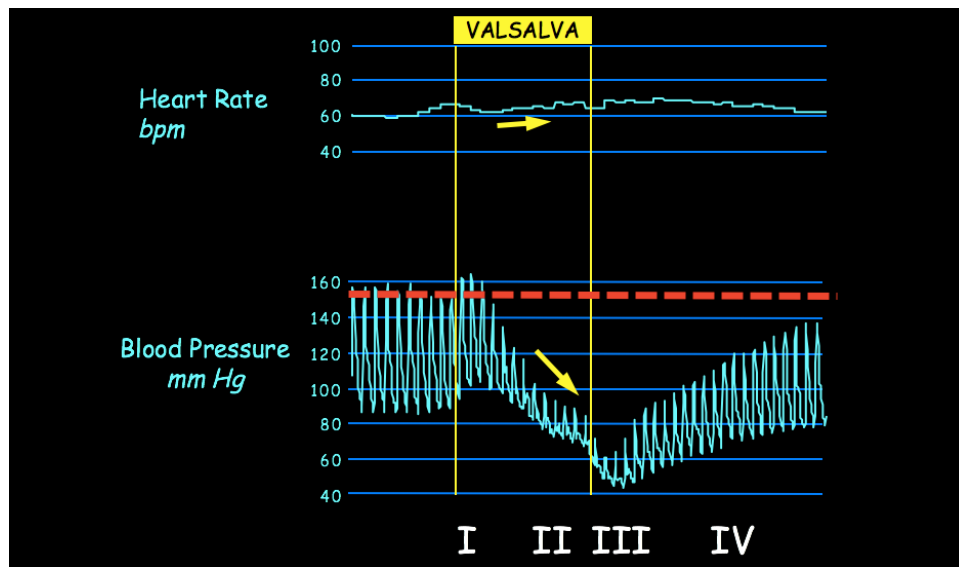
Then you relax. Momentarily, in Phase III the blood pressure falls—a kind of mirror image of the increase in Phase I. The decrease in pressure in Phase III has nothing to do with reflexes.

Finally, in Phase IV the patient is relaxed, and there is no impediment in blood getting to the heart. The heart pumps the blood, but it pumps the blood into the reflexively constricted vasculature, and so the blood pressure overshoots the baseline value. It's as if you turned the faucet back up to where it was originally, but you forgot to loosen the nozzle.

Because of the overshoot in pressure, the heart rate rapidly reflexively falls back to baseline.

In a patient with failure of this reflex, whether because there is a decrease in afferent information from the baroreceptors to the brain, or because the brain doesn't act on that information due a brain disease, or because the sympathetic nerves are gone, or because norepinephrine isn't released, or because the adrenoceptors receptors are blocked, you get the same abnormal pattern of blood pressure during and after the Valsalva maneuver. In Phase II the blood pressure goes down

progressively, because the patient can't tighten the vascular nozzle, and in Phase IV the pressure returns slowly to the baseline value but doesn't overshoot, for the same reason.



Abnormal blood pressure (BP) and heart rate (HR) responses to the Valsalva maneuver, indicating failure to regulate the sympathetic and parasympathetic nervous systems correctly.

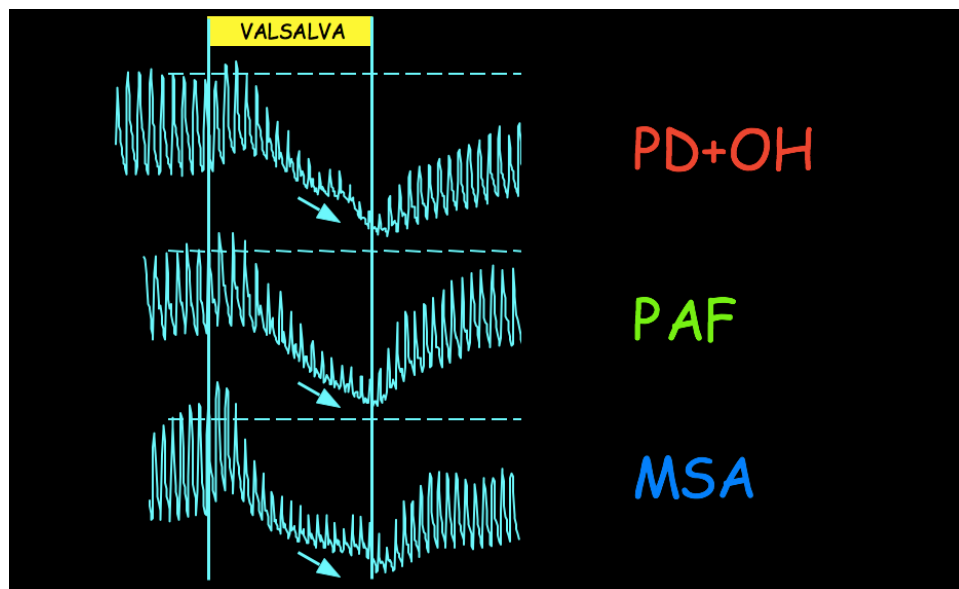
In most (but not all) forms of chronic autonomic failure manifesting with orthostatic hypotension, the heart rate doesn't change as much as it should given the magnitude of the fall in pressure. The extent of increase in heart rate (or more formally the extent of decrease in the interbeat interval) per mmHg decrease in systolic blood pressure during Phase II of the Valsalva maneuver is a measure of baroreflex-cardiovagal gain.

Note that one must monitor the blood pressure changes beat-to-beat in order to diagnose sympathetic neurocirculatory failure based on the Valsalva maneuver. Until recently, such monitoring required insertion of a catheter into an artery. Since

neurologists rarely feel comfortable doing this, they usually settle for recording only the peak and trough pulse rates during and after performance of the maneuver. This may enable a diagnosis of parasympathetic neurocirculatory failure but cannot diagnose sympathetic neurocirculatory failure.

Nowadays there are several non-invasive devices available to track blood pressure beat-to-beat and detect baroreflex-sympathoneural failure.

It is important to bear in mind that the finding of abnormal blood pressure responses to the Valsalva maneuver is valuable for diagnosing sympathetic neurocirculatory failure but is of no value in the differential diagnosis of autonomic failure syndromes.



The same abnormal pattern of beat-to-beat blood pressure occurs in different autonomic failure syndromes.

For instance, the same abnormal pattern occurs in Parkinson's

disease with orthostatic hypotension, pure autonomic failure, and multiple system atrophy.

TILT TABLE TESTING

Tilt table testing is done to see if standing up (orthostasis) provokes a progressive fall in blood pressure (orthostatic hypotension), a period of blood pressure instability followed by a sudden fall in blood pressure (neurally mediated hypotension), an excessive increase in pulse rate, as in postural tachycardia syndrome (POTS), or fainting (also known as autonomically mediated syncope, neurally mediated syncope, neurocardiogenic syncope, or reflex syncope).

The testing itself is relatively simple. The patient lies on a stretcher-like table, straps like seat belts are attached around the abdomen and legs, and the patient is tilted upright at an angle. The exact angle used varies from center to center and may be from 60 degrees to 90 degrees. The tilting goes on for up to about 40 minutes (this again varies from center to center).

For evaluating possible postural tachycardia syndrome or autonomically mediated syncope, a relatively long period of tilting is used. The tilting is a form of provocative test. The doctors are hoping to reproduce the patient's problem in a controlled laboratory situation. For evaluating possible orthostatic hypotension, 5 minutes of tilting is sufficient.

If the patient tolerates the tilting for this period, then the patient may receive a drug, such as isoproterenol or nitroglycerine, which may provoke a sudden fall in blood pressure or loss of

consciousness. (Most autonomic centers no longer do this, because of the possibility of false positive test results.)

As soon as the test becomes positive, such as by a sudden fall in blood pressure, the patient is put back into a position lying flat or with the head down. Sometimes fluid is given by vein. Consciousness, if lost, rapidly returns once the patient is put back down; however, symptoms such as a sense of imbalance, disorientation, clouded thinking, or headache can continue for hours or even days later.



Tilt table testing usually is done with a motorized tilt table.

The testing is quite safe when done by experienced personnel, in a setting where emergency backup is available.

Tilt table testing is used to evaluate patients with a complaint of fainting or inability to tolerate prolonged standing.

There are some disadvantages of tilt table testing. One is false-positive test results, especially when a drug is used. In a false-positive test, the results of the test are positive, but some healthy people can have a positive test result, so that a positive

test result might not actually mean that anything really is “wrong.”

A false-positive result could lead the doctor to conclude that the condition is fainting, a relatively benign situation, whereas the patient actually has a serious medical problem. This is what happened in the case of the basketball star Reggie Lewis, as discussed below, and the ironic case of one of his cardiologists, Dr. Thomas Graboys, discussed later.

Tilt table testing might also not reproduce the patient’s problem—a false-negative test result.

Another disadvantage is that most tilt table testing does not provide information about disease mechanisms. This means that, beyond verifying the patient’s complaints, the testing does little to suggest pathophysiologically rational treatments that might be effective.

“Augmented” tilt table testing involves measurements of physiological functions such as forearm vascular resistance and sampling blood for assays of levels of norepinephrine and adrenaline. Augmented testing can provide information about mechanisms; however, few centers offer this form of tilt table testing.

Standard tilt table testing is not very useful in patients with a persistent fall in blood pressure each time they stand up (orthostatic hypotension), because the results are a foregone conclusion: the blood pressure will fall progressively during the tilting. Augmented tilt table testing, however, can help determine if the orthostatic hypotension results from a

particular form of sympathetic nervous system failure. For instance, in a patient with orthostatic hypotension, if the plasma levels of norepinephrine and DHPG were normal during supine rest but failed to increase during tilting, the orthostatic hypotension could reflect failure to increase sympathetic noradrenergic system traffic reflexively.

The Reggie Lewis Case

Reggie Lewis was a star basketball player for the Boston Celtics. In game 1 of the 1993 Eastern Conference First Round of the NBA Playoffs, on April 29, 1993, he collapsed on the basketball court. He came back later and finished with 17 points. He was later evaluated by a 12-member cardiology “dream team” that included Dr. Thomas Graboys at the New England Baptist Hospital. They thought he had a form of cardiomyopathy and recommended that Lewis cease playing.

Needless to say, millions of dollars were at stake. Lewis went for a second opinion, which was provided by Dr. Gilbert Mudge of the Peter Bent Brigham Hospital. Mudge concluded that Lewis had “athlete’s heart” and neurocardiogenic syncope—benign conditions—and could resume playing.

Mudge’s assessment became one of the most widely publicized and second-guessed opinions in the annals of medicine. According to a New York Times article, a key procedure that led to Mudge’s opinion was a tilt table test. During head-up tilting at 60 degrees from horizontal, Lewis reported the same lightheadedness that he had experienced before collapsing on the Celtics’ NBA court.

The tilt table test yielded false-positive results. Before Lewis ever played another NBA game, while shooting hoops at Brandeis University on July 27, 1993 he collapsed again—and died.

He was autopsied and found to have an abnormal, enlarged, extensively scarred heart, but the exact cause of death was never made public. His death was attributed variously to hypertrophic cardiomyopathy, a viral myocarditis, or even cocaine cardiotoxicity.

A lawsuit filed by the widow against Mudge resulted in a mistrial.

The take-home lesson is that Reggie Lewis had a false-positive tilt table test.

The story of the Reggie Lewis case leads ironically to the story of one of his cardiologists, Dr. Thomas Graboys. The Graboys case is discussed in the section on dementia with Lewy bodies.

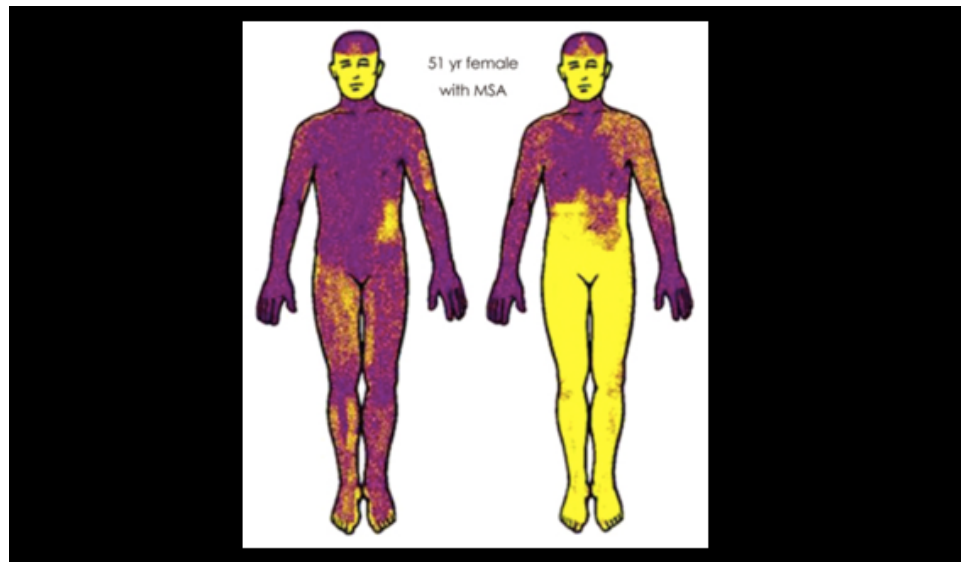
Sweat Tests

Sweating is an important way people regulate body temperature in response to external heat. The brain increases sweating by directing an increase in sympathetic cholinergic system (SCS) traffic to sweat glands in the skin. The chemical messenger, acetylcholine, is released, the acetylcholine occupies muscarinic receptors on the sweat glands, and the glands secrete sweat.

One can examine SCS function from the sweating response to

external heat (thermoregulatory sweat test, TST).

Sweat tests evaluate a particular part of “automatic” nervous system function.



Sweating assessed by the indicator powder test (courtesy of P. Low)

Sweat production can be visualized by sprinkling starch with iodine or other indicator powder (e.g., alizarin red) all over the body. When the powder is wetted, the powder turns color. One can then photograph the body and see which parts sweated. This sort of sweat testing can be informative in detecting small fiber neuropathy, sympathetic cholinergic denervation in the feet or hands, or denervation in large areas of the trunk.

When the skin becomes sweaty, the ability to conduct electricity increases because of the salt and water in the sweat, and one can monitor the electrical conductivity. Sweating also

increases local humidity, and one can monitor the humidity in a chamber strapped to a limb and applied to the skin. One can also take pictures of sweat droplets or obtain a latex impression of the droplets to quantify the amount of sweating.

The galvanic skin response (GSR), or skin sympathetic test (SST), is part of polygraphic “lie detector” testing. When a person is startled, or a small electric shock is delivered, increased SCS (and possibly sympathetic adrenergic system) activity evokes sweating.

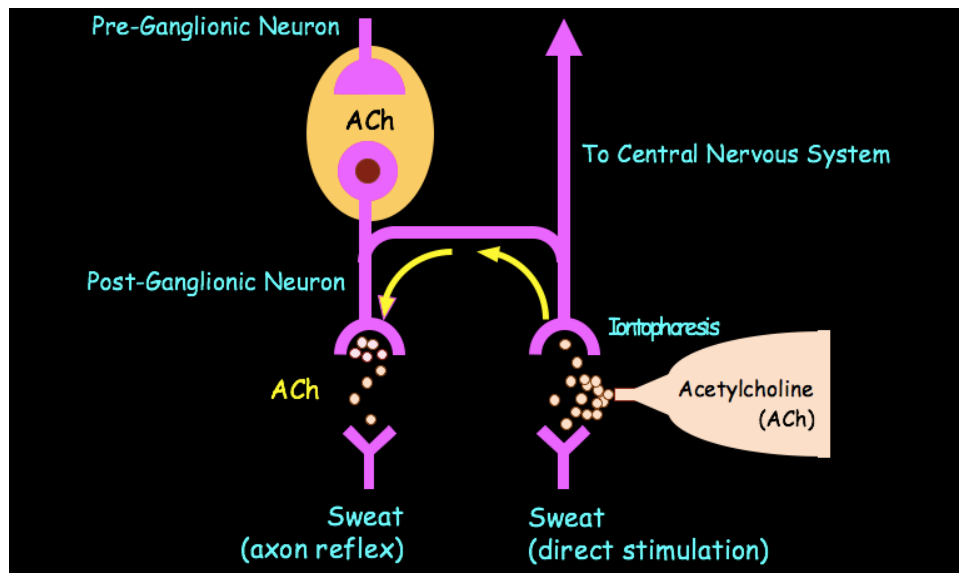
Advantages of these sweat tests are that they are generally safe, simple, and quick. A disadvantage is that they mainly or only measure physiological changes as a result of release of acetylcholine from sympathetic nerves. That is, they assess only one component of the autonomic nervous system. There are some forms of dysautonomia (dopamine-beta-hydroxylase deficiency and Parkinson’s disease with orthostatic hypotension are examples) where the patients have normal sweating.

The TST cannot distinguish sympathetic cholinergic denervation from a lesion in central neural pathways involved with thermoregulation, and carrying out the TST requires a specialized heat chamber that is not available at many centers. Drugs that block receptors for acetylcholine are used commonly for urinary problems, and these drugs can interfere with results of the test.

The QSART

“QSART” stands for “Quantitative Sudomotor Axon Reflex Test.”

This test is a form of sweat test. Sweating in response to altered environmental temperature results from the effects of the chemical messenger, acetylcholine, released from sympathetic nerve terminals near sweat glands in the skin. The QSART is a test of the ability of sympathetic nerves in the skin to release acetylcholine and increase sweat production.



The QSART is a special form of sweat test.

In the QSART procedure, dried air is pumped at a controlled rate through a small plastic capsule placed on the skin. When the person sweats, the humidity in the chamber increases. This provides a measure of sweat production.

For QSART testing, acetylcholine is applied to the skin surrounding the capsule, by a special procedure called iontophoresis. The locally applied acetylcholine evokes sweating at the site where it is given, but in addition, by way of a type of reflex called an axon reflex, sympathetic nerves under the plastic capsule release the body's own acetylcholine. This

results in sweat production measured by increased humidity in the capsule.

If a person had a local loss of sympathetic cholinergic nerves, then applying acetylcholine to the skin around the test capsule would not lead to increased sweating or increased humidity in the test capsule, although the acetylcholine would increase sweating directly where it was applied. If the person had a brain disease that prevented increases in sympathetic cholinergic nerve traffic during exposure to increased environmental temperature, then the person would not be able to increase the humidity in the capsule in response to an increase in the room temperature, and yet the person would have a normal QSART response.

By this sort of neuropharmacologic test, doctors can distinguish sympathetic cholinergic system failure due to loss of sympathetic cholinergic nerves from failure due to abnormal regulation of nerve traffic in intact nerves.

Advantages of the QSART are that it is generally safe, quick, quantitative, and easy to perform. There are also several disadvantages. The equipment required is expensive. As in other tests where the key factor being measured is physiological (in this case, sweat production), the results are indirect. For instance, if the patient had a problem with the ability to make acetylcholine in the nerve terminals, with the ability of acetylcholine to bind to its receptors in the sweat glands, or decreased numbers of sweat glands, the patient would have the same abnormal QSART responses as if the sympathetic cholinergic nerves were lost. QSART results may or may not identify problems in regulation of the heart and blood vessels

by other parts of the autonomic nervous system. In other words, the QSART results might not be representative.

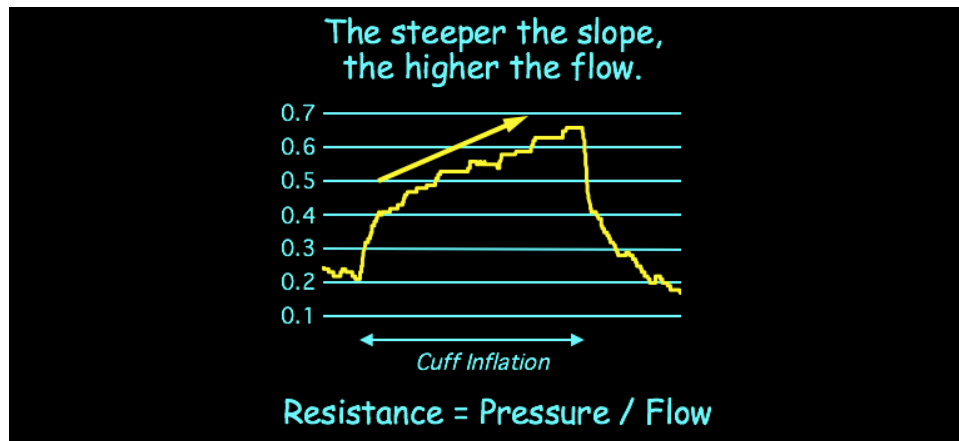
QSART testing is a useful way to detect loss of nerve fibers in the feet, as occurs in small fiber neuropathies and “neuropathic” POTS.

FOREARM BLOOD FLOW

Blood flow in the forearm can be measured non-invasively using an automated blood pressure cuff and a bracelet-like device.

Measuring forearm blood flow is useful to test whether the patient tightens blood vessels reflexively, as normally happens during assumption of upright posture.

To measure forearm blood flow one can use a technique called impedance plethysmography. A blood pressure cuff is wrapped around the upper arm, and a special bracelet-like device called a strain gauge is attached around the upper forearm. The strain gauge measures stretch very sensitively. For a measurement of forearm blood flow, the blood pressure cuff is inflated rapidly using a special cuff inflator to just above the venous pressure but below the diastolic blood pressure (typically 40 mmHg). This is like tightening a tourniquet around the upper arm to obtain a blood sample. Because the cuff pressure is above the venous pressure, blood in the forearm and hand can't get past the cuff, and because the cuff pressure is below the arterial pressure, blood can still enter the forearm and hand. In this



One way to measure forearm blood flow is a method called impedance plethysmography.

situation, the volume of the forearm expands slightly, and the strain gauge senses the increase in volume.

If the rate of blood flow into the forearm were high, then the volume of the forearm would increase rapidly after the cuff was inflated; and if the rate of blood flow were low, then the volume of the forearm would increase more slowly. By a simple calculation you can estimate the blood flow into the forearm, from the rate of increase in the volume of the forearm after the cuff is inflated. Usually, measurement of forearm blood flow is done at least five times over about a minute, to obtain a reliable average value.

Once the rate of forearm blood flow (FBF) is known, the forearm vascular resistance (FVR) is calculated from the average blood pressure (mean arterial pressure, MAP) divided by the forearm blood flow. This is a similar calculation as for measuring total peripheral resistance (TPR) from the mean arterial pressure (MAP) divided by the cardiac output (CO). In

the garden hose analogy referred in the presentation of the Valsalva maneuver, the FVR would correspond to the extent of tightening of the vascular “nozzle.”

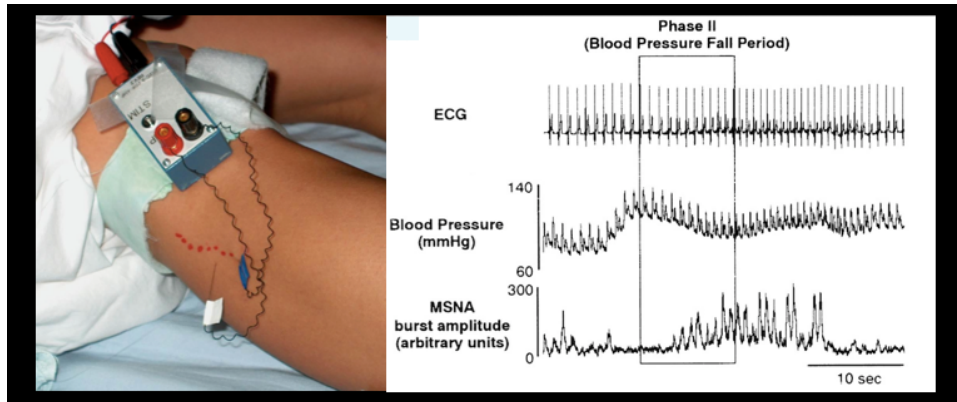
When you stand up, the forearm vascular resistance normally increases. This is because of reflexive activation of the sympathetic noradrenergic system. When a person stands up or is tilted on a tilt table as part of tilt-table testing, the amount of blood ejected by the heart per minute falls, due to the force of gravity, which tends to pool blood in the legs and lower abdomen pelvis and decreases venous return to the heart. The brain directs an increase in sympathetic noradrenergic system outflows, norepinephrine is released from nerve terminals in blood vessel walls in the forearm and hand, and the forearm vascular resistance (FVR) goes up. In sympathetic neurocirculatory failure, the FVR doesn't increase like it should and may not increase at all. In fainting, the FVR typically decreases, due to adrenaline-induced relaxation of blood vessels in skeletal muscle. In patients with low blood volume, FVR may be high even during supine rest, as part of a compensation to maintain blood pressure.

SYMPATHETIC MICRONEUROGRAPHY

One can monitor sympathetic noradrenergic outflow to skeletal muscle via a needle electrode inserted into the peroneal nerve, which is in the “funny bone” outside and just below the knee. Sometimes the measurement in abbreviated MSNA, for muscle sympathetic nerve activity.

Bursts of MSNA are related to baroreflex function. The bursts

are tied to the heartbeat and are called “pulse-synchronous.” When the blood pressure decreases, MSNA increases reflexively, due to activation of sympathetic noradrenergic system outflow to the blood vessels in the skeletal muscles. The frequency of pulse-synchronous bursts goes up.



During the Valsalva maneuver, the decrease in blood pressure in Phase II is associated with a reflexive increase in bursts of skeletal muscle sympathetic nerve traffic.

An advantage of monitoring MSNA is the ability to track SNS responses to a variety of stimuli rapidly and in real time; however, carrying out MSNA measurements requires substantial technical training and experience, and the measurements may not be covered by medical insurance.

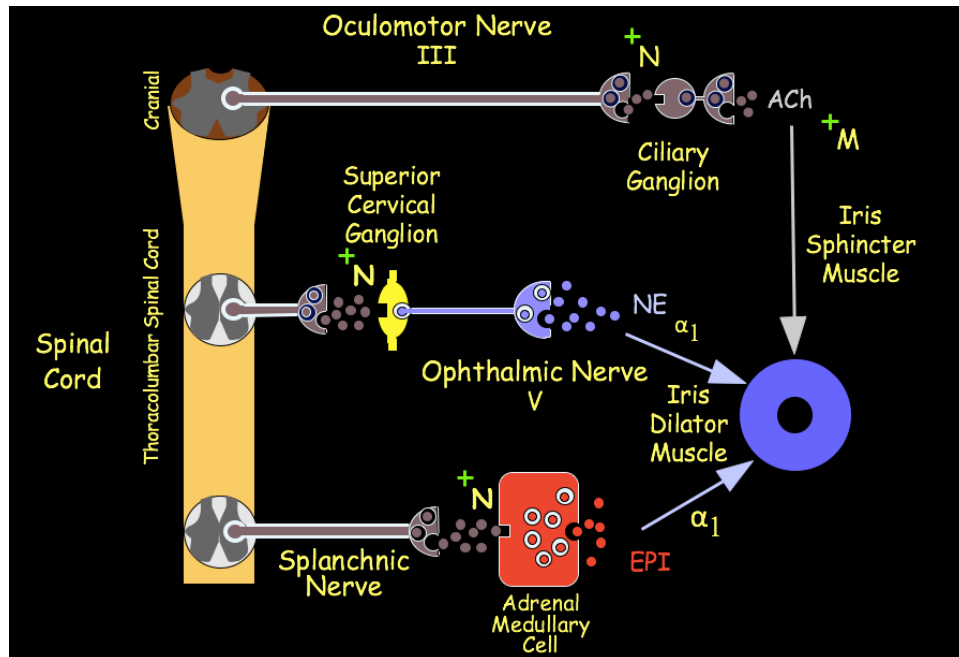
Identifying nerve traffic as MSNA often requires assessing effects of baroreflex activation or inhibition on the signal, such as by breath holding or performing a Valsalva maneuver. In patients with chronic autonomic failure, MSNA can be difficult to measure because of the lack baroreflex-mediated, pulse-synchronous bursts of nerve traffic.

Sympathetic noradrenergic outflow to the skin is not so

sensitive to baroreflexes and is more sensitive to psychological phenomenon such as startle.

PUPILLOMETRY

The pupils of the eyes receive both parasympathetic nervous system (PNS) and sympathetic noradrenergic system (SNS) innervation.



The PNS innervation of the pupils is derived from the Edinger-Westphal nucleus, located in the midbrain of the brainstem. The nerve fibers synapse in the ciliary ganglion and travel with the oculomotor nerve to the iris sphincter muscle. The SNS innervation of the pupils is derived from the superior cervical ganglion. The nerve fibers travel in the ophthalmic nerve to the iris dilator muscle.

Pupil constriction evoked by PNS stimulation is mediated by

acetylcholine acting at muscarinic receptors on iris sphincter muscle cells. The nerve fibers travel in the oculomotor nerve, which is the third cranial nerve, via the ciliary ganglion. The sphincter muscle cells are arranged circularly in the iris, and so when they contract the pupil gets smaller.

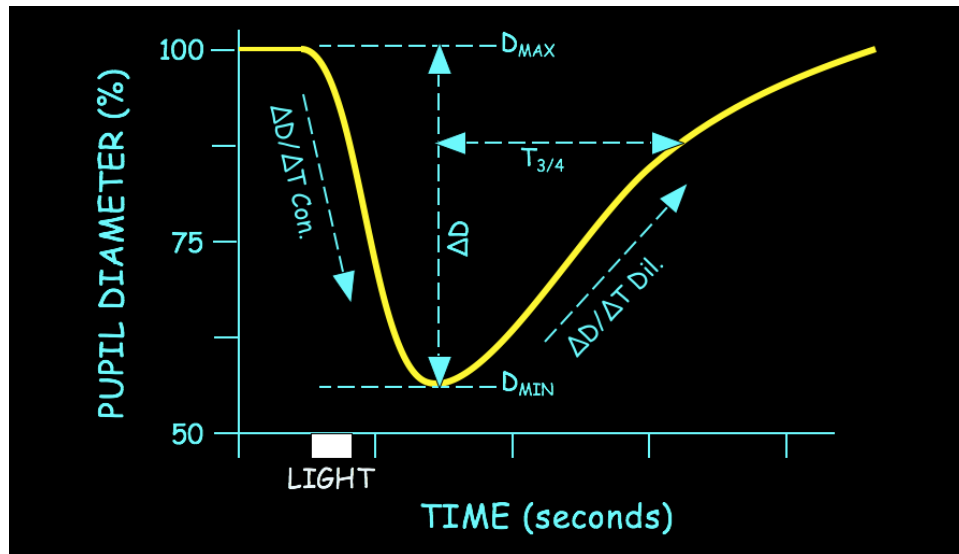
The SNS innervation of the pupils is derived from pre-ganglionic neurons in the thoracic spinal cord. The nerve fibers synapse in the superior cervical ganglion in the neck and travel with the ophthalmic nerve, which is part of the fifth cranial nerve (the trigeminal nerve).

The pupil dilation evoked by SNS stimulation is mediated by norepinephrine acting at alpha-1 adrenoceptors on iris dilator muscle cells. The iris dilator cells are arranged radially (like spokes on a bicycle wheel) in the iris, and so when they contract the pupil gets larger.

Activation of the sympathetic adrenergic system (SAS), such as during distress, causes release of adrenaline into the bloodstream. Adrenaline also acts at the alpha-1 adrenoceptors on iris dilator muscle cells and dilates the pupils. SAS activation probably explains the pupil dilation that occurs when people faint. The pupillary light reflex is too rapid to involve adrenaline.

Pupillometry involves tracking the dynamics of pupil size in response to a brief light stimulus. This is a simple, non-invasive autonomic function test. In response to a brief light stimulus, the pupils constrict, due to a rapid increase in PNS activity. After the light stimulus, the pupils slowly re-dilate. The rate of re-dilation seems to involve a contribution of the

SNS, since patients with Horner's syndrome (discussed below) not only have a small pupil but also have been reported to have a delay in the return of pupil diameter toward baseline (prolonged $T_{3/4}$ in the diagram).



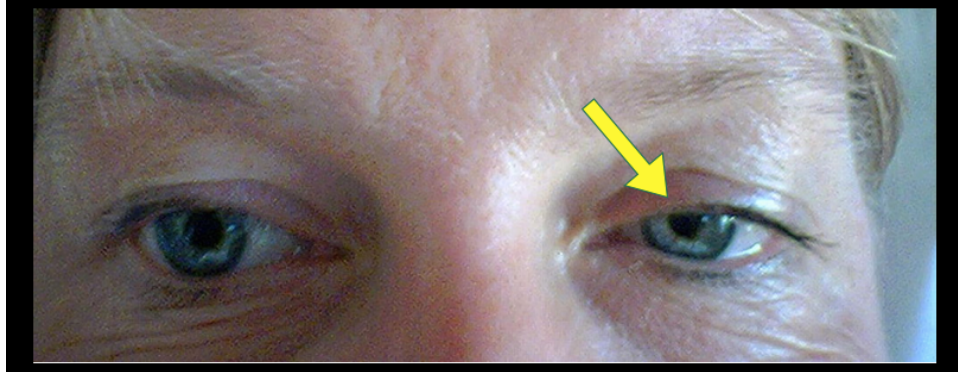
Pupil diameter responses to a brief light stimulus

How pupillometry results relate to abnormalities of particular components of the autonomic nervous system in dysautonomias is a matter of current research.

Horner's Syndrome

Horner's syndrome (also called Horner-Bernard and Bernard-Horner syndrome, depending on your loyalty to Claude Bernard) involves the triad of ptosis (lid lag), miosis (constricted pupils), and anhidrosis (lack of sweating) on the affected side of the face.

Horner's syndrome usually reflects loss of input from the sympathetic noradrenergic system (SNS) and sympathetic cholinergic system (SCS), while PNS effects on the pupils are unopposed.



Horner's syndrome. There are a droopy eyelid (ptosis), a smaller pupil (miosis), and decreased sweating. The eye on the affected side also seems sunken in (enophthalmos).

Sympathetic nerves to the face travel from the thoracic spinal cord through ganglia before ascending in the chest and neck to the head. A tumor in the chest or neck that involves the sympathetic chain can manifest clinically as Horner's syndrome.

Adie's Pupil

In people with Adie's "tonic" pupil, the affected pupil is relatively large and constricts slowly in bright light. The condition begins gradually in one eye and often progresses to involve the other eye.

When Adie's pupil is associated with a loss deep tendon reflexes, this is called Holmes-Adie syndrome, and when in

addition there is altered sweating, this is called Ross's syndrome.

As for the tonic pupil, in Holmes-Adie syndrome the loss of deep tendon reflexes (especially of the Achilles tendon) may occur first on one side of the body and then go on to involve the other side too. The eye and reflex symptoms may not appear at the same time. In Ross's syndrome, the loss of sweating can be associated with increased sweating and flushing on the other side of the face, in which case Ross's syndrome can overlap with the "harlequin syndrome," which is discussed elsewhere.

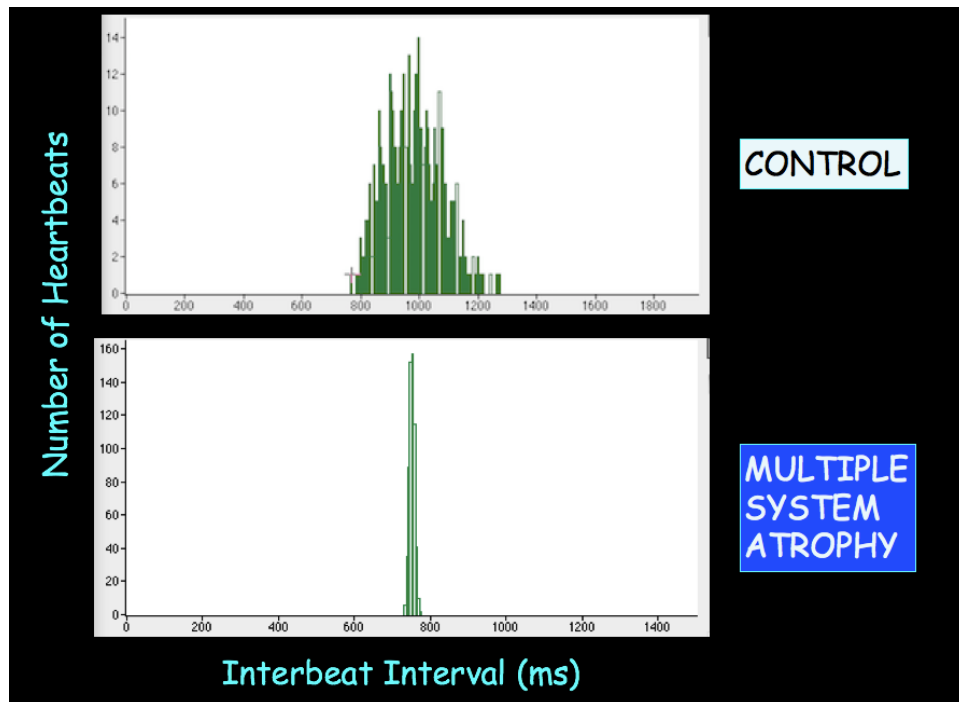
Ross's syndrome is thought to result from a viral infection that damages sensory neurons in the dorsal root ganglia and autonomic neurons in the ciliary ganglia. The complex involvement of skin sensory and autonomic innervation results in abnormal thermoregulatory changes in sweating and skin blood flow. The syndrome can be an isolated finding or occur with other conditions such as Sjogren's syndrome, migraine, or baroreflex failure. Once it develops, the syndrome is long-lasting or permanent.

HEART RATE VARIABILITY

The Sign of a Healthy Heart

When you take in a slow, deep breath, your pulse rate normally increases, and when you then breathe out, your pulse rate falls. The wave-like rhythmic change in the heart rate due to breathing is called respiratory sinus arrhythmia.

Despite the word, arrhythmia, meaning “lacking rhythm,” respiratory sinus arrhythmia is quite rhythmic and quite normal. These changes result mainly from modulation of vagus nerve traffic to the heart. The famous Dutch cardiologist, Karel Frederik Wenckebach, wrote in the early 1900s that a variable pulse rate is the sign of a healthy heart.



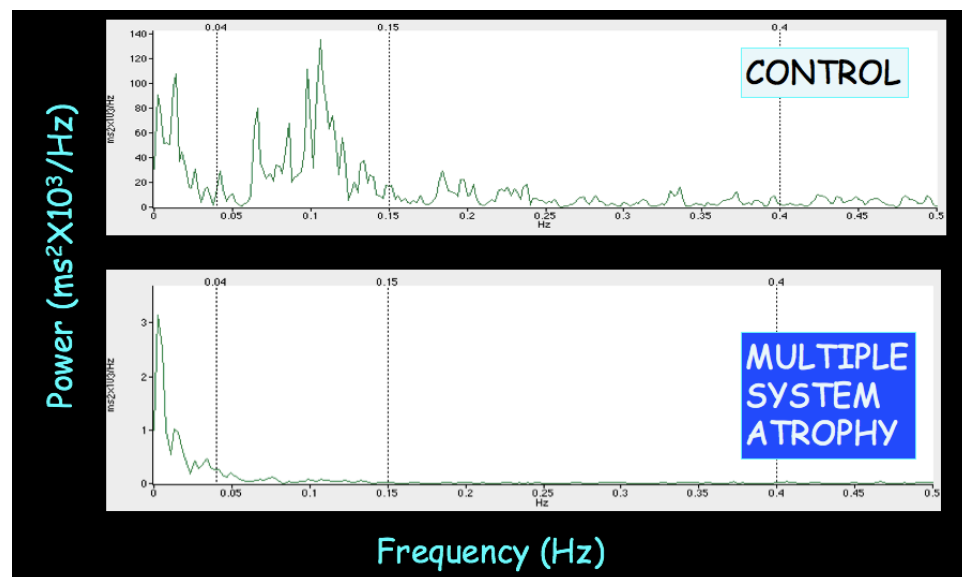
Heart rate variability in the time domain. Chronic autonomic failure syndromes such as multiple system atrophy involve low heart rate variability.

If you recorded the cardiac interbeat interval across many heartbeats and graphed the number of beats in bins of interbeat intervals, you would see a bell-shaped curve. The more variable the heart rate, the wider the bell-shaped curve. This is called analysis of heart rate variability in the time domain.

With aging, many forms of heart disease such as congestive heart failure, and in most forms of chronic autonomic failure, the heart rate becomes more stable. The bell-shaped curve becomes narrower. This is probably not from altered autonomic innervation of the heart but from decreased reflexive modulation of traffic in autonomic nerves supplying the heart.

Power Spectral Analysis

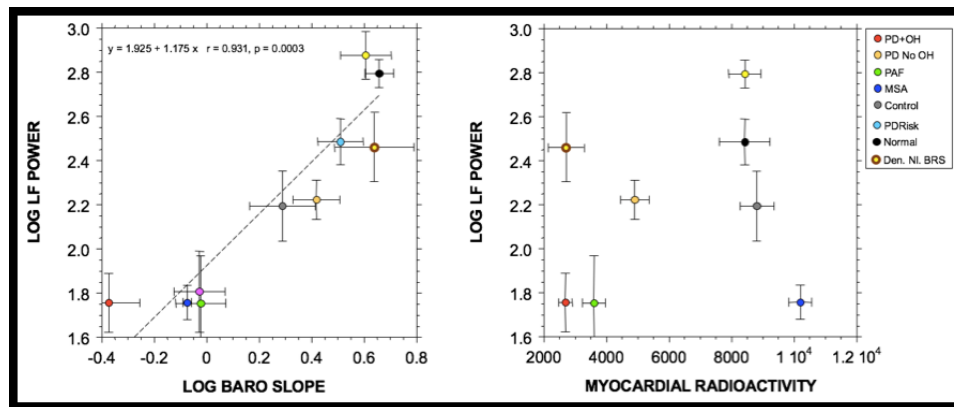
This test is much simpler than the fancy name suggests. Normally, a person's heart rate is not constant. The pulse rate increases when the person breathes in and then decreases when the person breathes out.



Heart rate variability in the frequency domain. At all frequencies there is low power in multiple system atrophy.

This means that the pulse rate normally oscillates in a wave-like pattern. Another form of analysis of heart rate variability is in

the frequency domain. If one graphed the size of the oscillation as a function of the frequency of the heartbeats, then at the frequency of breathing, which is about once every 8 seconds, corresponding to 8/60 or 0.13 cycles per second (Hertz), there would a peak of “power.” In people who have failure of the parasympathetic nervous system, there is little or no respiratory sinus arrhythmia, and so there is no peak of power at the frequency of breathing.



Across a variety of dysautonomias the low frequency power is related to baroreflex function but not to sympathetic innervation of the heart.

This sort of analysis typically reveals a second peak of power, at a lower frequency than the frequency of breathing.

Researchers have thought that low frequency power of heart rate variability is related to sympathetic nervous system influences on the heart; however, the parasympathetic nervous system also affects low frequency power. Other researchers have disagreed with the notion that power spectral analysis of heart rate variability can assess sympathetic innervation of the heart and have proposed instead that low frequency power is more a measure of the ability to modulate autonomic outflows

to the heart by way of the baroreflex. Strong support for this view comes from the fact that across a variety of dysautonomias the log of low frequency power is related to the log of baroreflex-cardiovagal gain.

Power spectral analysis of heart rate variability offers the advantages of being safe, technically easy, and fast. The main disadvantage is that the meanings of low frequency power (and of the low:high frequency ratio, proposed to reflect “sympathovagal balance”) remain unsettled.

AMBULATORY BLOOD PRESSURE MONITORING

Ambulatory blood pressure monitoring, or ABPM, refers to automatic recording of blood pressure at pre-set time intervals during activities of daily life.

ABPM can be valuable to assess whether the patient has the normal “dipping” of blood pressure that occurs during the night. Non-dipping often occurs in patients with neurogenic orthostatic hypotension, because during the day the patients have relatively low blood pressure when they are upright, and at night they have relatively high blood pressure when they are lying down (nocturnal hypertension).

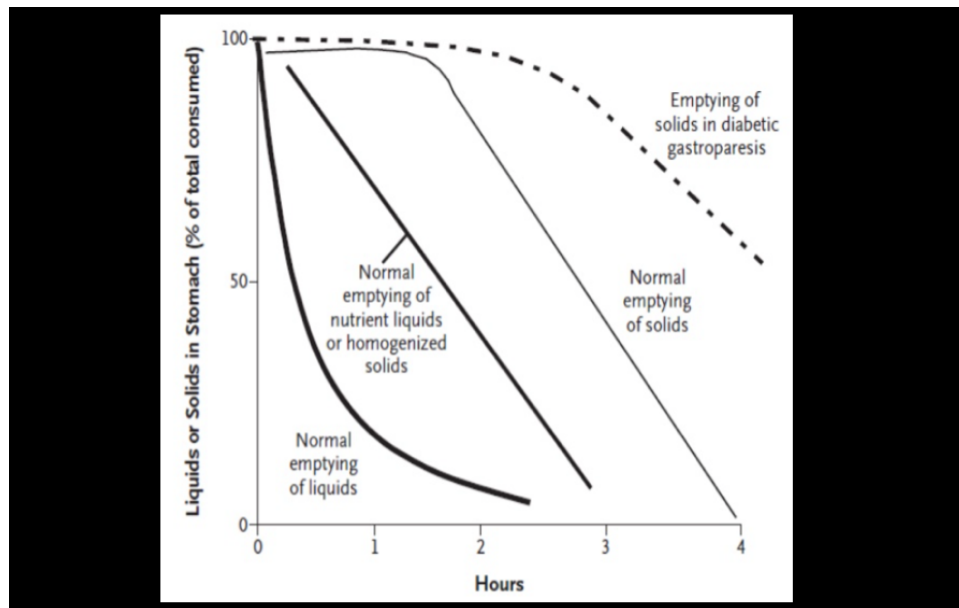
Ambulatory blood pressure monitoring can be used to detect high blood pressure at night (nocturnal hypertension).

ABPM is quite useful to assess variability of blood pressure over many hours of observation. Patients with arterial baroreflex failure typically have large swings of blood pressure during the day and night.

Some patients have “white coat hypertension,” meaning their blood pressures are high in the doctor’s office but are normal at home. ABPM can help diagnose white coat hypertension.

GASTRIC EMPTYING

Many autonomic, endocrine, and local factors regulate stomach emptying after ingestion of a meal.



Normally, about ½ of ingested solid food passes through the stomach by 2-3 hours. Liquids pass through quicker.

One clinical test of gastric emptying is based on nuclear

medical scanning after swallowing a substance tagged with radioactivity.

The term, “gastroparesis,” refers to delayed gastric emptying due to poor stomach motility. A decreased rate of gastric emptying can be a sign of parasympathetic cholinergic failure, sympathetic noradrenergic system hyperactivity, increased circulating adrenaline levels, or any of a variety of endocrine or local enteric neuronal abnormalities.

Damage to the vagus nerve supplying the stomach can result from gastric surgery. Probably the most common disorders involving gastroparesis are diabetes mellitus, Parkinson’s disease, and multiple sclerosis.

THE COLD PRESSOR TEST

In the cold pressor test, blood pressure is monitored when the patient dunks a hand into a bucket of ice-cold water and keeps the hand immersed. This rapidly increases the blood pressure by increasing activity of the sympathetic noradrenergic system. In a patient with baroreflex failure and an intact sympathetic noradrenergic system, the cold pressor test would be expected to evoke an exaggerated increase in blood pressure, while in a patient with baroreflex failure and sympathetic noradrenergic denervation the pressor response would be blunted.

The cold pressor test can only be done for a minute or two. The stimulus is complex and dynamic because of the rapid development of pain, numbness, and distress. Patients with dysautonomia associated with burning pain in the skin

(erythromelalgia) can have a remarkable ability to tolerate prolonged cold pressor testing.

COMPOSITE AUTONOMIC SEVERITY SCALE

Autonomic laboratory checklists have been developed with the goal of aiding the diagnostic workup, following the disease course, tracking responses to treatments, and research. Findings are weighted in terms of orthostatic intolerance, sexual failure, bladder disorder, diarrhea, gastroparesis, secretomotor disorder, constipation, vasomotor disorder, and pupillomotor disorder. A 10-point composite autonomic severity scale (CASS) allots 4 points for “adrenergic failure” and 3 points each for “sudomotor failure” and “cardiovagal” failure. Patients with a CASS score of 3 or less have no or mild autonomic failure, 4-6 moderate autonomic failure, and 7-10 severe autonomic failure.

This kind of lumped approach to autonomic failure may be more worthwhile for research purposes than for individual diagnosis. The CASS is insensitive to failure of single components of the autonomic nervous system, such as in dopamine-beta-hydroxylase (DBH) deficiency. The prevalence in the relevant population is not taken into account—constipation in the elderly is common, while pupillomotor dysfunction is uncommon. Within a particular domain, subtle differences can be crucial for differential diagnosis—urinary bladder dysfunction is found in both Parkinson’s disease with orthostatic hypotension (PD+OH) and in the parkinsonian form of multiple system atrophy (MSA-P), but urinary retention requiring self-catheterization is common in MSA-P and rare in

PD+OH. The term, “adrenergic failure,” is misleading, since no measure of sympathetic adrenergic (as opposed to sympathetic noradrenergic) failure is included. The composite scale also depends importantly on the particular center. Neurochemical and neuroimaging tests that can be more sensitive and informative than physiological tests are not included.

Drug Tests

TYRAMINE

In the tyramine (TYR) infusion test, the drug tyramine is infused intravenously (IV). TYR taken up into the sympathetic nerves displaces norepinephrine

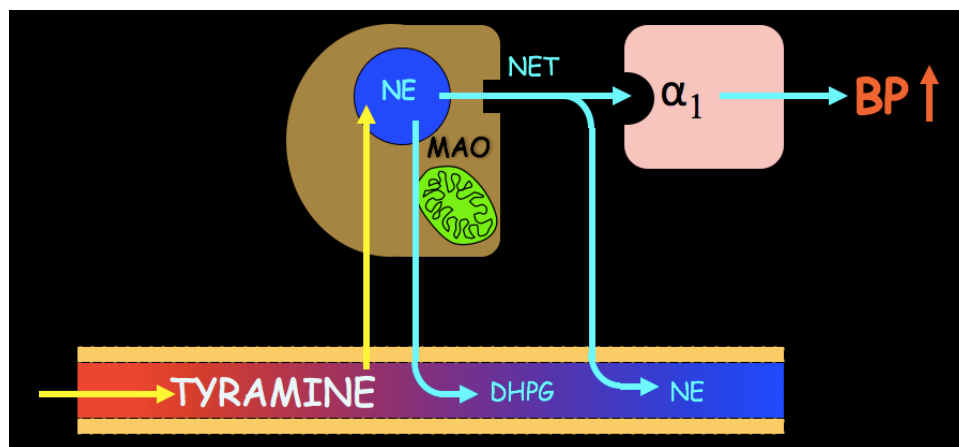


Diagram of the tyramine (TYR) infusion test.

(NE) from the vesicles. Some of the NE reaches its receptors on vascular smooth muscle cells, and the blood pressure goes up. Plasma NE and its breakdown product DHPG may also be measured.

Tyramine is a chemical that is found in some dietary constituents, such as hard cheese and red wine. Normally tyramine that is ingested is broken down in the gut and produces no effects on the body; however, if you are on a drug that interferes with this breakdown, then the tyramine can enter the bloodstream.

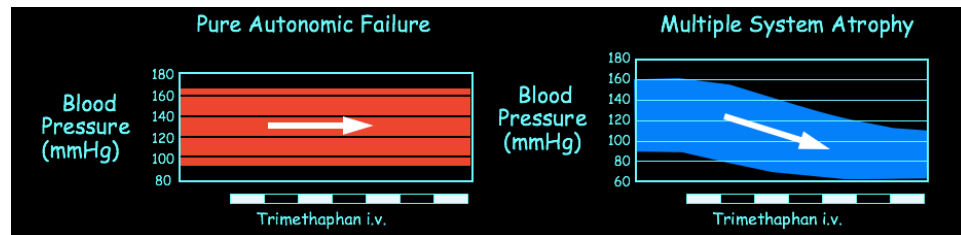
If a patient had autonomic failure due to a loss of sympathetic nerves, tyramine would not release norepinephrine from the nerves, because there would be no norepinephrine to displace. In such a patient tyramine would not increase the blood pressure by as much as if the patient had an intact sympathetic noradrenergic system. In addition, such a patient would have relatively small increases in levels of norepinephrine and related compounds, such as dihydroxyphenylglycol (DHPG), in the plasma.

The enzyme that breaks down tyramine in the gut is called monoamine oxidase (MAO). MAO inhibitors are used to treat some psychiatric or neurological disorders. If a patient on an MAO inhibitor were to ingest foodstuffs containing tyramine, the tyramine could displace norepinephrine from its stores in the sympathetic nerves and increase blood pressure to a dangerously high level—a phenomenon called the “cheese effect.”

In patients who have autonomic failure with intact sympathetic nerves, the doctor might actually exploit the cheese effect, by prescribing a combination of tyramine with an MAO inhibitor.

There are two forms of MAO, MAO-A and MAO-B. MAO-B inhibitors are used to treat Parkinson’s disease. MAO-B inhibitors are much less likely than MAO-A inhibitors to interfere with the breakdown of tyramine, because in the gut and sympathetic nerves tyramine breakdown is mainly by MAO-A. Patients treated with MAO-B inhibitors are not prone to the cheese effect.

GANGLION BLOCKADE



Effects on blood pressure of injection of the ganglion blocker, trimethaphan, in a patient with pure autonomic failure (PAF), and in a patient with multiple system atrophy (MSA).

Trimethaphan, pentolinium, and hexamethonium are ganglion blockers—that is, they block transmission of nerve signals in the ganglia. The control signals are relayed in the ganglia by release of the chemical messenger, acetylcholine, which binds to nicotinic receptors on the post-ganglionic neurons. Stimulation of the nicotinic receptors, such as by nicotine itself, increases post-ganglionic nerve traffic in both the parasympathetic and sympathetic nervous systems and releases adrenaline from the adrenal gland.

Trimethaphan, pentolinium, and hexamethonium block neuronal nicotinic receptors. By blocking the receptors, they inhibit the transmission of nerve impulses in the ganglia to the post-ganglionic nerves of the sympathetic and parasympathetic nervous systems.

Because of the blockade of transmission of nerve impulses in ganglia, these drugs produce clear effects on a variety of body functions. When a person stands up, the ability to maintain blood pressure depends importantly on reflexes that tighten blood vessels by way of increased sympathetic noradrenergic

nerve traffic. Ganglion blockers always produce a fall in blood pressure when the person is upright—orthostatic hypotension—and blunt or eliminate reflexive increases in heart rate. If the person were lying down at the time, the drugs produce smaller decreases in blood pressure.

Probably the most noticeable effect of ganglion blockade in someone who is lying down is a dry mouth. This is because of blockade of the parasympathetic nervous system, which is responsible for production of watery saliva.

In the ganglion blockade test, a ganglion blocker drug is given by vein at a dose calculated so as not to decrease the blood pressure excessively. The blood pressure and pulse rate are monitored frequently or continuously, and blood may be sampled from an indwelling catheter in an arm vein, for measurements of plasma levels of norepinephrine or other neurochemicals.

If a patient had autonomic failure due to a loss of sympathetic nerves, such as in pure autonomic failure, there would be no release of norepinephrine from the nerve terminals, because of the absence of the terminals. Ganglion blockade in such a patient would not decrease the blood pressure. But if a patient had autonomic and baroreflex failure due to a brain disease in which there was an inability to regulate sympathetic nerve traffic to intact terminals, there might be ongoing, unregulated release of norepinephrine from the nerve terminals. Ganglion blockade in such a patient would decrease the blood pressure excessively, as in multiple system atrophy. The ganglion blockade test therefore can provide information about whether autonomic failure is associated with a loss of sympathetic nerve

terminals or from failure of the brain to regulate sympathetic nerve traffic appropriately.

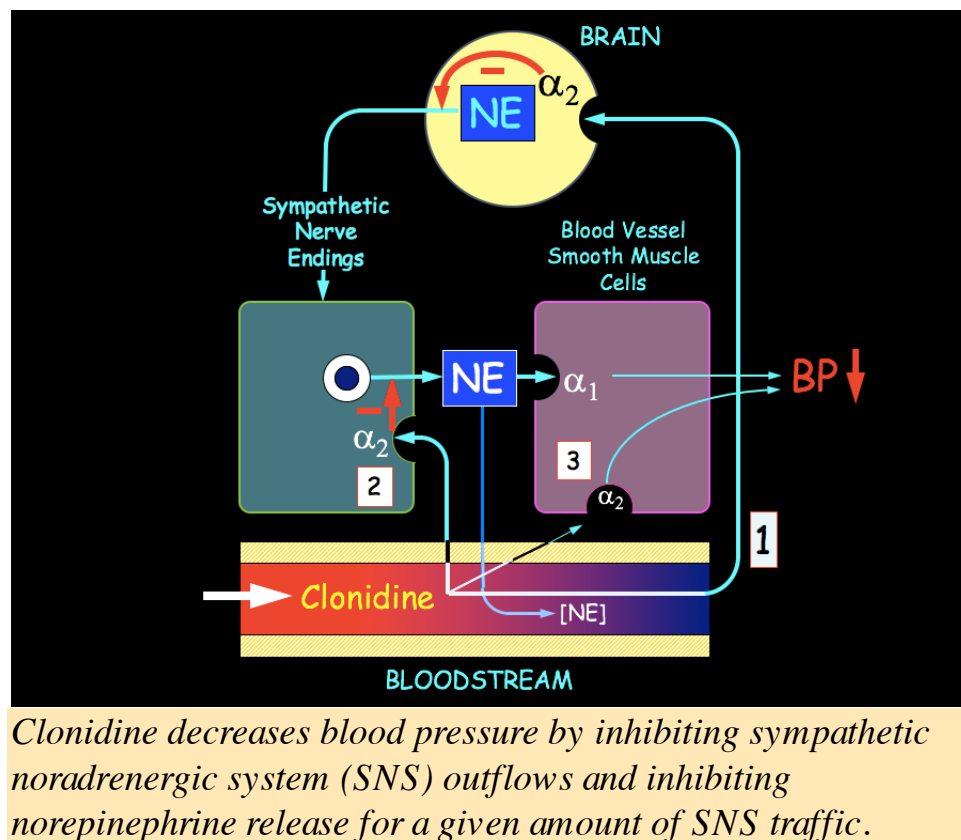
In some patients with long-term high blood pressure, the hypertension reflects an overall increase in the rate of nerve traffic in the sympathetic noradrenergic system. This increases delivery of norepinephrine to its receptors in the heart and blood vessels, causing an increase in the output of blood by the heart (cardiac output) and tightening of blood vessels (vasoconstriction). By either or both mechanisms, the blood pressure is high because of the high rate of delivery of norepinephrine to its receptors. Some investigators have called this hypernoradrenergic hypertension. In a patient with hypernoradrenergic hypertension, infusion of a ganglion blocker would be expected to decrease the rate of norepinephrine release from the sympathetic nerves, and the extent of the fall in the plasma norepinephrine level would be related to the extent of the fall in blood pressure. In a patient with an equal amount of hypertension but with a normal rate of nerve traffic in the sympathetic noradrenergic system, ganglion blockade would not be expected to decrease the blood pressure so much.

Because ganglion blockers are potent inhibitors of the sympathetic and parasympathetic nervous systems, the drugs must be given at a carefully determined dose, by personnel who are well acquainted with their effects. If the dose were too high, then the blood pressure (especially the systolic blood pressure) could fall too much. The effects of ganglion blockade wear off fairly quickly—more quickly for trimethaphan than for pentolinium.

Unfortunately, ganglion blockers are not available commercially any more.

CLONIDINE

Clonidine (brand name Catapres™) stimulates alpha-2 adrenoceptors in the brain, in blood vessel walls, and on sympathetic nerve terminals. Clonidine decreases release of norepinephrine from sympathetic nerves and decreases blood pressure.



The clonidine suppression test is based on effects of the drug on blood pressure and on plasma levels of norepinephrine. If a

patient had excessive activity of the sympathetic noradrenergic system, then clonidine would produce large decreases in blood pressure and plasma norepinephrine levels. Clonidine suppression testing therefore can identify long-term high blood pressure associated with increased release of norepinephrine from sympathetic nerve terminals—hypernoradrenergic hypertension.

Clonidine suppression testing is used mainly to evaluate possible pheochromocytoma, a tumor that produces catecholamines. In pheochromocytoma plasma norepinephrine fails to decrease after clonidine administration, due to continuous, unregulated norepinephrine secretion by the tumor.

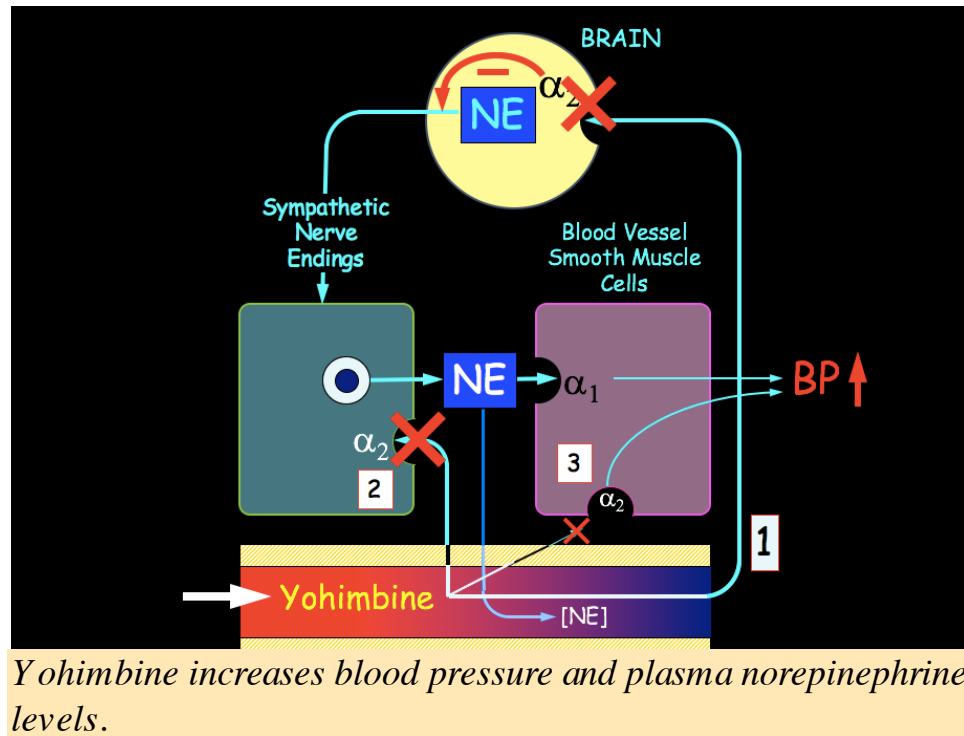
YOHIMBINE

Yohimbine is a type of alpha-2 adrenoceptor blocker. Alpha-2 adrenoceptors are receptors for norepinephrine that exist at high concentrations in certain parts of the brain, on sympathetic nerves, and in blood vessel walls. Alpha-2 adrenoceptors on sympathetic nerves act like a brake on norepinephrine release from the terminals. When alpha-2 adrenoceptors on sympathetic nerves are blocked, this increases the amount of norepinephrine release for a given amount of sympathetic nerve traffic.

By blocking alpha-2 adrenoceptors in the brain and on sympathetic nerve terminals, yohimbine releases norepinephrine from the terminals. The released norepinephrine binds to alpha-1 adrenoceptors in blood vessel walls, increasing the blood pressure. Yohimbine also blocks

alpha-2 receptors on vascular smooth muscle cells, but this effect is minor compared to the effects in the brain and on sympathetic nerve terminals.

In the yohimbine challenge test, the drug is given by vein for several minutes or given by mouth as a single dose. The blood pressure and pulse rate are monitored frequently or continuously, and blood is sampled from an indwelling catheter, for assays of plasma levels of norepinephrine and other neurochemicals.



Because of the blockade of alpha-2 adrenoceptors in the brain, infused yohimbine can produce any of several behavioral or emotional effects, which vary from person to person. Yohimbine can cause an increase in alertness or feelings such as anxiety or sadness, or, on the other hand, happiness or a

sense of energy. Rarely, yohimbine infusion can evoke a panic attack; however, in my experience patients informed about the neurobehavioral effects of yohimbine and reassured that the effects are temporary do not report emotional changes as a result of the test.

Yohimbine infusion usually causes trembling, which sometimes is so severe that the teeth chatter. It also causes paleness of the skin, goosebumps, and piloerection (hair bristling), as if the person felt cold or distressed. Actually, the body temperature does not fall at all, and the person does not feel cold.

In hypertensive patients, the finding of a large increase in blood pressure coupled with a large increase in the plasma norepinephrine level during the yohimbine challenge test supports a diagnosis of hypernoradrenergic hypertension.

In patients who have decreased activity of the cell membrane norepinephrine transporter, or NET, when yohimbine releases norepinephrine from the sympathetic nerves the released norepinephrine is not inactivated by reuptake of the norepinephrine back into the nerve terminals. This results in excessive delivery of norepinephrine to its receptors, both in the brain and outside the brain. In patients with NET deficiency, yohimbine produces large increases plasma norepinephrine and blood pressure. In such patients yohimbine infusion can also evoke panic or chest pain or pressure that mimic the chest pain or pressure in coronary artery disease.

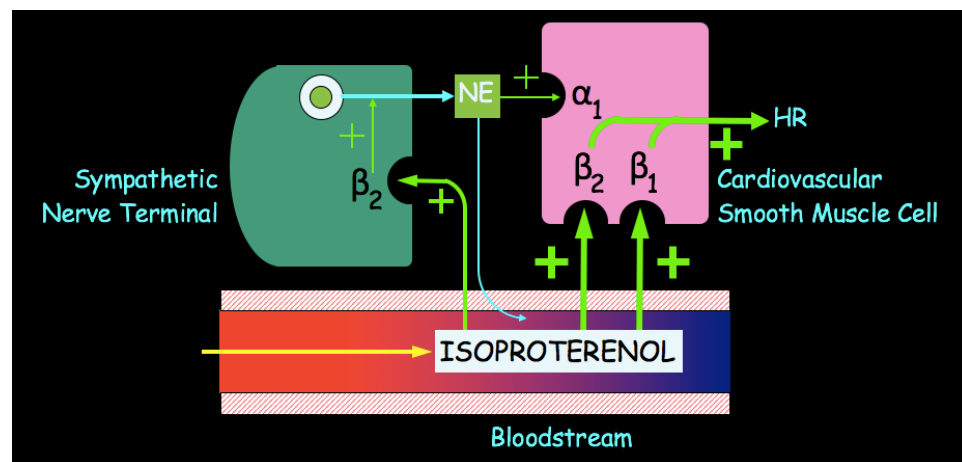
The yohimbine challenge test can provide useful information about whether autonomic failure is associated with a loss of

sympathetic nerves or from failure of the brain to regulate sympathetic nerve traffic appropriately. In pure autonomic failure, yohimbine exerts relatively small effects on blood pressure or plasma norepinephrine levels, whereas in multiple system atrophy yohimbine produces large increases in both.

The yohimbine challenge test should be done only by personnel who are well acquainted with its effects in different forms of dysautonomia.

ISOPROTERENOL

The isoproterenol infusion test can help identify causes of abnormal heart rate or inability to tolerate prolonged standing.



Isoproterenol stimulates beta-adrenoceptors. By way of norepinephrine release, it also indirectly stimulates alpha-adrenoceptors.

Isoproterenol (brand name Isuprel™) stimulates beta-adrenoceptors. Because of this action, isoproterenol has several effects in the body. Stimulation of beta-adrenoceptors in the

heart increases the rate and force of the heartbeat and increases the output of blood by the heart per minute (cardiac output). Stimulation of beta-adrenoceptors in the bronchioles, the small airway tubes in the lungs, opens them and therefore can reverse acute asthma attacks. Stimulation of beta-adrenoceptors in the liver converts stored energy in the form of glycogen to immediately available energy in the form of glucose. Stimulation of beta-adrenoceptors in blood vessel walls of skeletal muscle relaxes the blood vessels, and this decreases the resistance to blood flow in the body as a whole (total peripheral resistance). Stimulation of beta-adrenoceptors on sympathetic nerves increases the release of norepinephrine.

Isoproterenol is infused by vein as part of diagnostic testing for a few types of dysautonomias.

The isoproterenol infusion test can help identify causes of abnormal heart rate or inability to tolerate prolonged standing.

In the hyperdynamic circulation syndrome, the patient has a relatively fast pulse rate, high cardiac output, a variable blood pressure that tends to be high, susceptibility to panic or anxiety attacks, and improvement by treatment with the beta-adrenoceptor blocker, propranolol. The same holds true for many relatively young patients with early, borderline hypertension. Such patients have excessive increases in pulse rate in response to isoproterenol given by vein.

Patients with the postural tachycardia syndrome (POTS) can have a fast pulse rate even when they are lying down. In POTS

patients, isoproterenol can produce excessive increases in heart rate or evoke panic.

Isoproterenol given by vein is also sometimes used as part of tilt table testing in patients with chronic fatigue syndrome. During upright tilting, infusion of isoproterenol can bring on a rapid fall in blood pressure or loss of consciousness, converting a negative tilt table test to a positive tilt table test. This brings up the issue of how frequently a healthy person might have one of these reactions in response to isoproterenol infusion while tilted—a false-positive result.

Isoproterenol releases norepinephrine from sympathetic nerves. Patients with a form of dysautonomia associated with a loss of sympathetic nerves would be expected to have a blunted increase in the plasma norepinephrine level in response to isoproterenol. This is what happens, for instance, in Parkinson's disease with orthostatic hypotension.

The effects of isoproterenol wear off rapidly within minutes of stopping the infusion. The drug does not cross the blood-brain barrier, and so usually there are few if any behavioral or emotional responses. Isoproterenol can increase the rate or depth of respiration, produce trembling, or bring on abnormal heart rhythms or abnormal heartbeats. These side effects disappear rapidly after the drug is stopped.

GLUCAGON

Glucagon is one of the body's three main hormones regulating glucose levels.

When given intravenously (IV) as a bolus, glucagon stimulates release of adrenaline from the adrenal medulla. In patients with an adrenal gland tumor that makes catecholamines (pheochromocytoma, or “pheo”), glucagon challenge testing can produce a large increase in blood pressure.

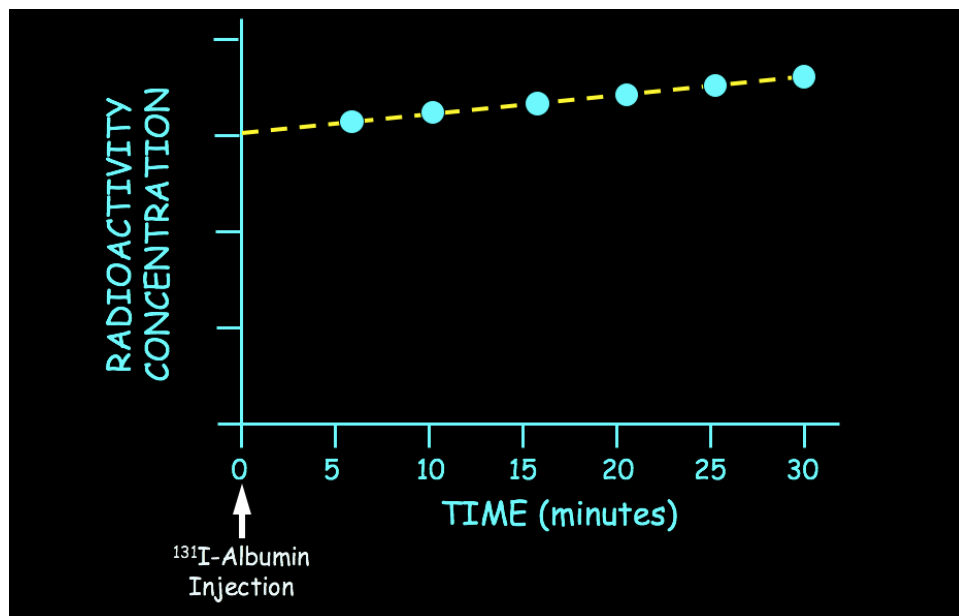
Glucagon challenge testing is also used in the evaluation of patients who seem to have a pheo clinically but who don't actually harbor the tumor. These patients are thought to have “pseudopheochromocytoma,” or “pseudopheo.” The condition can resemble postural tachycardia syndrome, arterial baroreflex failure, or hyperdynamic circulation syndrome. Glucagon administration in pseudopheo patients can evoke a large increase in plasma adrenaline levels. This constitutes a positive glucagon challenge test.

¹³¹I-ALBUMIN TO MEASURE BLOOD VOLUME

Blood volume is the total volume of blood in the body. Most of the blood volume is in veins. When a person stands up, blood pools in the legs, pelvis, and abdomen due to gravity. If the blood volume were low, then because of gravitational blood pooling there would be less blood returning to the heart to pump to body organs including the brain, and the person could feel lightheaded or faint.

In patients with chronic orthostatic intolerance, measurement of blood volume may be indicated, since if the blood volume were low, a drug such as fludrocortisone and a high salt diet might benefit the patient by increasing the blood volume.

There are different ways to measure blood volume. A commercially available test is based on intravenous (IV) injection of albumin that is tagged with a trace amount of radioactive iodine (^{131}I -albumin). Albumin is the main protein in the blood. In the ^{131}I -albumin blood volume test, an exact, known amount of ^{131}I -albumin is injected. Most of the injected ^{131}I -albumin stays in the bloodstream. Blood is drawn through the IV, and the concentration of ^{131}I in the plasma is measured. By definition, the concentration of a substance is the amount



In the blood volume test, blood volume is calculated from the concentration and amount of a drug in the bloodstream.

of the substance per unit of volume. Since the amount of ^{131}I injected is known, and the plasma concentration of ^{131}I is measured in the laboratory, by algebra the plasma volume is the ^{131}I concentration divided by the amount of injected ^{131}I . From the plasma volume divided by the hematocrit (the percent of the

blood that is red blood cells), the blood volume is then calculated.

Because the concentration of ^{131}I -albumin in the blood may change slightly over time (such as by leakage out of the blood vessels), blood is sampled at several time points, and the concentration that is estimated to be present in the blood immediately after injection is used for the calculation of blood volume.

Biochemical Tests

Neurochemical tests of autonomic nervous system functions are mainly done to examine activities of the sympathetic noradrenergic system (SNS) and the sympathetic adrenergic system (SAS). This is because the main chemical messengers of these systems, norepinephrine and epinephrine (adrenaline), can be measured in the plasma, whereas the main chemical messenger of the parasympathetic nervous system, acetylcholine, undergoes rapid enzymatic breakdown and cannot be measured in the plasma.

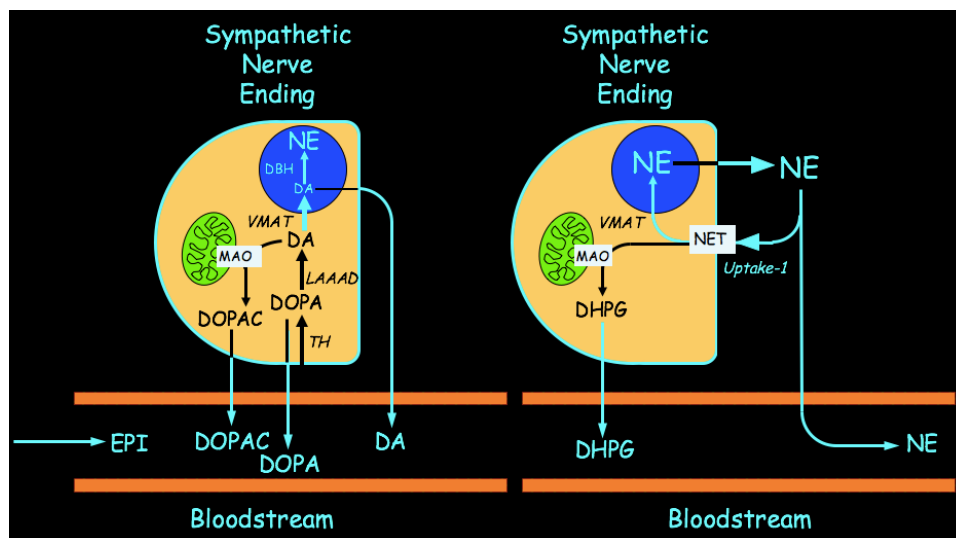
THE CAT COMES BACK

Human plasma normally contains at least 6 catechols. Three are the catecholamines dopamine, norepinephrine, and adrenaline (epinephrine, EPI). Another is DOPA (also known as levodopa), which is the precursor of the catecholamines and the immediate product of the enzymatic rate-limiting step in catecholamine biosynthesis. Two others are dihydroxyphenylglycol (DHPG), which is the main neuronal metabolite of norepinephrine, and dihydroxyphenylacetic acid (DOPAC), which is the main neuronal metabolite of dopamine.

The actual chemical, catechol, doesn't exist in the body. I use the term, catechols, to refer to chemicals that have the catechol structure in them. As I hope you recall, catechols looks like the head of a cat.

Dopamine depletion in a particular brain pathway causes the movement disorder in Parkinson's disease; however, plasma

dopamine is unrelated to dopamine in the brain. At least some of plasma dopamine is derived from vesicles in sympathetic noradrenergic nerves, presumably because of exocytotic release from the vesicles before the dopamine has had a chance to be converted to norepinephrine. Plasma dopamine levels normally are very low—as little as a few picograms (a millionth of a



Human plasma contains at least 6 catechols—the catecholamines NE, EPI, and DA, the catecholamine precursor DOPA, the DA metabolite DOPAC, and the NE metabolite DHPG.

millionth of a gram) per milliliter.

Norepinephrine (NE) is the main chemical messenger of the sympathetic noradrenergic system (SNS) and is also a neurotransmitter in the brain. Plasma and cerebrospinal NE levels are related to each other, despite a blood-brain barrier for NE. This relationship indicates an association between NE release in the brain and SNS outflow. The exact basis for this relationship is unknown.

Epinephrine, or adrenaline, is the hormone of the sympathetic adrenergic system (SAS). Adrenaline is produced from norepinephrine by the actions of a few co-factors and the enzyme, phenylethanolamine-N-methyltransferase, abbreviated PNMT. S-Adenosyl-methionine acts as the methyl group donor for the reaction. Importantly, cortisol is trophic for the actions of PNMT. This is a key link between two of the body's main distress systems, the SAS and the hypothalamic-pituitary-adrenocortical system.

Norepinephrine is produced from dopamine by the enzyme dopamine-beta-hydroxylase, or DBH. DBH is localized to the storage vesicles in the sympathetic noradrenergic nerves. Therefore, in order to produce norepinephrine, dopamine in the cytoplasm must be taken up into the vesicles. In the vesicles the dopamine is converted to norepinephrine via DBH.

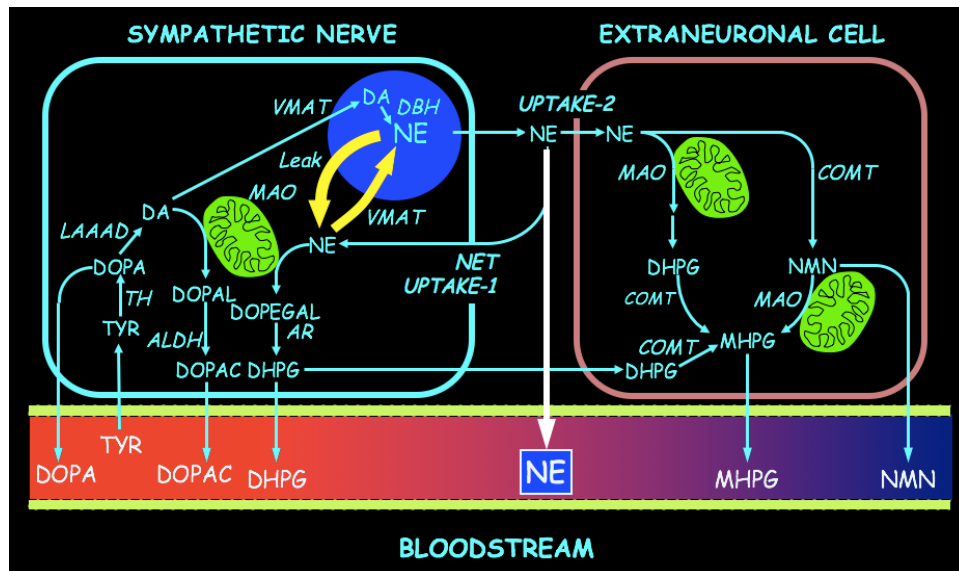
PLASMA NOREPINEPHRINE (NE)

Since norepinephrine (NE) is the main chemical messenger of the sympathetic noradrenergic system, doctors have often used the plasma norepinephrine level as an index of sympathetic noradrenergic system “activity” in the body as a whole. In people who are resting lying down, plasma NE levels normally range from about 100 to about 500 pg/mL.

Plasma norepinephrine is used to test the part of the sympathetic nervous system that regulates the heart and blood vessels—the sympathetic noradrenergic system.

The relationship between the rate of sympathetic nerve traffic

and the concentration of norepinephrine in the plasma is complex and indirect and is influenced by many factors such as commonly used drugs and activities of daily life. The blood sample should be obtained under carefully controlled or monitored conditions, and the plasma NE level should be interpreted by an expert.



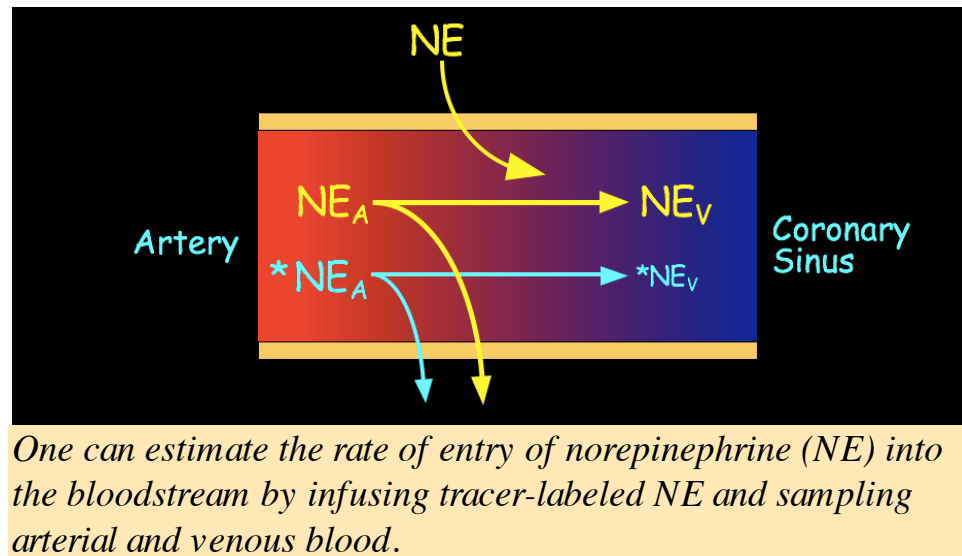
Determinants of plasma norepinephrine levels

Here is a brief description of some of the complexities involved:

First, only a small percent of the norepinephrine released from sympathetic nerves actually makes its way into the bloodstream. Most is recycled back into the nerve terminals, by the Uptake-1 process mediated by the cell membrane norepinephrine transporter, or NET. This means that a person might have a high plasma norepinephrine level, despite a normal rate of sympathetic nerve traffic, if the NET were

blocked by a drug or weren't working right.

Second, the plasma norepinephrine level is determined not only by the rate of entry of norepinephrine into the plasma but also by the rate of removal of norepinephrine from the plasma. Norepinephrine is cleared from the plasma extremely rapidly (half-time about 1.5 minutes). This means that a person might have a high plasma norepinephrine level because of a problem with the ability to remove norepinephrine from the plasma, such as in kidney failure.



One way to estimate the rate of norepinephrine entry into the bloodstream ("spillover") after taking plasma clearance into account is based on intravenous (IV) infusion of a tracer-labeled form of norepinephrine. The person's own norepinephrine, which is not labeled, dilutes the tracer-labeled norepinephrine. The more dilution of the tracer, the greater the norepinephrine spillover.

The tracer dilution technique cannot distinguish norepinephrine (NE) release from NE reuptake as determinants of NE spillover. Simultaneous measurement of levels of tracer-labeled NE and DHPG during infusion of tracer-labeled NE can do this. To the extent neuronal uptake of the tracer-labeled NE were decreased, formation of tracer-labeled DHPG from tracer-labeled NE would be decreased. If there were an increase in NE release without a change in reuptake, then the rate of NE spillover would be increased without a change in formation of tracer-labeled DHPG.

In using plasma norepinephrine levels to indicate activity of the sympathetic noradrenergic system, several complicating factors must be taken into account.

Third, norepinephrine is produced in sympathetic nerve terminals by the action of three enzymes, in concert with other required chemicals such as vitamin C, vitamin B6, and oxygen. In addition, norepinephrine is produced in, stored in, and released from tiny bubble-like “vesicles” in sympathetic nerves. For norepinephrine to be produced in the vesicles requires another transporter, called the “vesicular monoamine transporter,” or “VMAT.” If there were problem with any of these enzymes, co-factors, or the VMAT decreased norepinephrine production could result, and there would be a low plasma norepinephrine level, regardless of the rate of sympathetic nerve traffic.

Fourth, the plasma norepinephrine level usually is measured in a blood sample drawn from a vein in the arm. Because the skin and skeletal muscle in the forearm and hand contain

sympathetic nerves, the plasma norepinephrine level in blood from an arm vein is determined not only by the amount of norepinephrine release from sympathetic nerves in the body as a whole but also by release locally in the forearm and hand.

Fifth, the plasma norepinephrine level depends importantly on the posture of the person at the time of blood sampling (the level normally approximately doubles within 5 minutes of standing up from lying down), the time of day (highest in the morning), whether the person has been fasting, the temperature of the room, dietary factors such as salt intake, and any of a large number of commonly used over-the-counter and prescription drugs or herbal remedies. These factors often are not regulated or monitored.

PLASMA EPINEPHRINE (EPI)

Compared to the plasma norepinephrine level, which is complexly and indirectly related to sympathetic noradrenergic system “activity” in the body as a whole, the plasma epinephrine (adrenaline) level is a fairly direct indicator of activity of the sympathetic adrenergic system (also called the adrenomedullary hormonal system).

Plasma adrenaline (epinephrine) is used to test the sympathetic adrenergic system (SAS).

Nevertheless, some factors can complicate interpreting plasma adrenaline levels. When the forearm vascular resistance is high, EPI in arterial blood is extracted in passage through tissues of the arm, and in this setting the EPI level in the arm

venous plasma substantially underestimates the level in the arterial plasma.

A large number of common and difficult to control life experiences influence activity of the sympathetic adrenergic system. These include drugs, alterations in blood glucose levels (such as after a meal), body temperature, posture, and especially emotional distress.

Plasma EPI is probably the most sensitive biochemical index of distress.

An additional problem is technical. Adrenaline is a very powerful hormone. Predictably, the plasma adrenaline level normally is very low—so low that it is often below the limit of detection of commercial laboratory assays. In a healthy person lying down, plasma EPI levels can be as low as a few picograms (a millionth of a millionth of a gram) per milliliter.

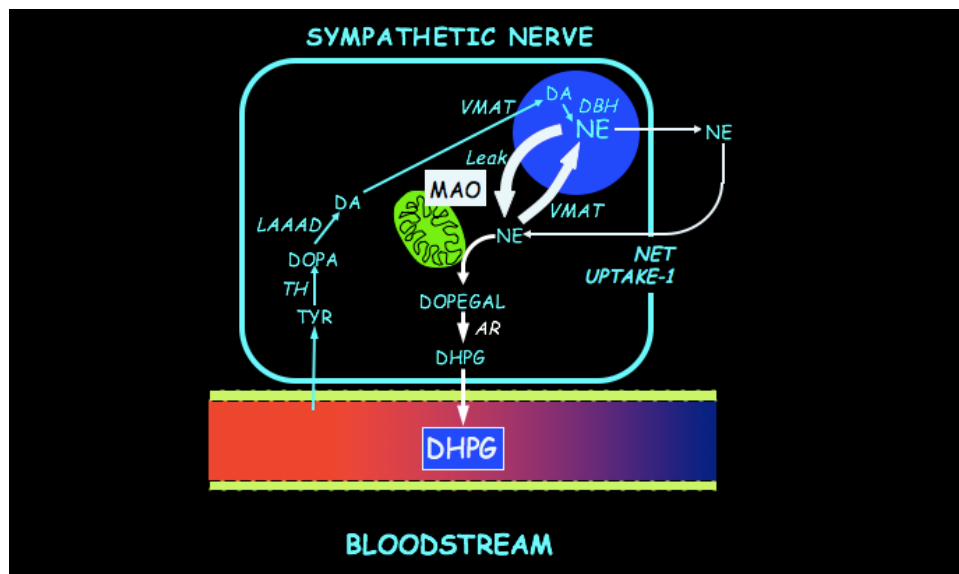
Other chemicals besides adrenaline can interfere with the measurement. This can especially be a problem in people who drink a lot of coffee, even if it is decaffeinated, because of chemicals in the plasma that can mimic adrenaline in the assay procedure.

Because of these issues, it is important that blood sampling and chemical assays for plasma adrenaline levels be carried out by experienced and expert personnel.

PLASMA AND CSF DHPG

3,4-Dihydroxyphenylglycol (DHPG, DOPEG) is the main neuronal metabolite of norepinephrine (NE). In people who are at rest lying down, plasma DHPG averages about 500-1,200 pg/mL.

Plasma DHPG levels provide important supplementary information in assessing the sympathetic noradrenergic system.



Plasma DHPG provides an index of stores of norepinephrine in sympathetic noradrenergic nerves.

Plasma DHPG levels have somewhat different determinants from plasma NE levels. Plasma NE levels are determined importantly by exocytotic release of NE in response to sympathetic nerve traffic and by neuronal reuptake via the cell membrane norepinephrine transporter (NET) via the Uptake-1

process.

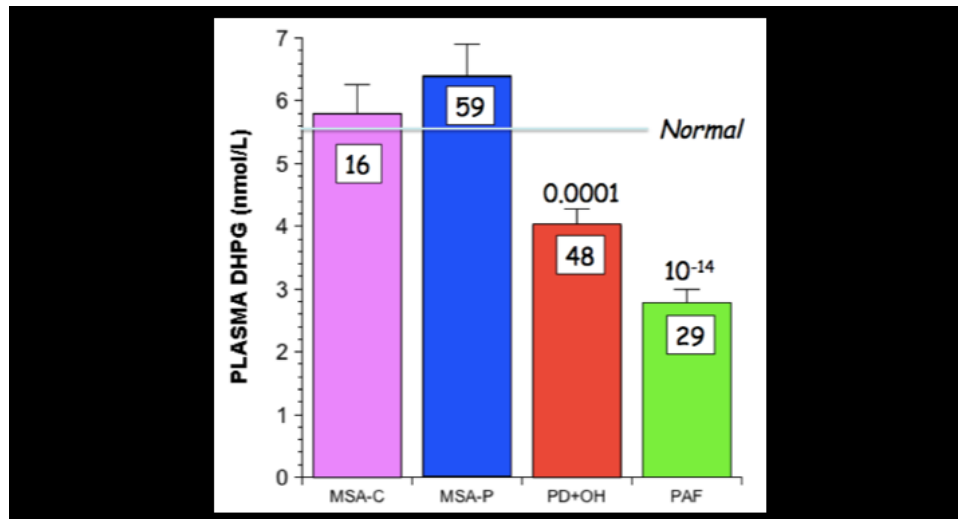
Under resting conditions, plasma DHPG levels are determined mainly by the net leakage of NE stored in vesicles and by monoamine oxidase (MAO) activity in sympathetic noradrenergic nerves.

In the setting of increased sympathetic noradrenergic system (SNS) activity, the increase in NE release results in an increase in plasma NE levels. This is what happens, for instance, during standing up (orthostasis). Plasma NE levels normally double within 5 minutes of standing up from lying down (normal increase at least 60%). Plasma DHPG levels also increase, due to reuptake of some of the released NE, but by a much smaller percent than the increase in plasma NE.

Plasma DHPG is better than plasma norepinephrine as measure of sympathetic noradrenergic innervation in the body as a whole.

In the setting of loss of SNS terminals, such as occurs in pure autonomic failure, there is a loss of NE stores, and plasma DHPG levels are decreased. Meanwhile, probably because of compensatorily increased SNS traffic in the residual nerves, plasma NE levels can be maintained.

Thus, in pure autonomic failure, which is known to be associated with substantial SNS denervation, plasma DHPG levels can be decreased more than NE levels.



Plasma DHPG is normal in MSA, often decreased in PD+OH, and almost always decreased in PAF

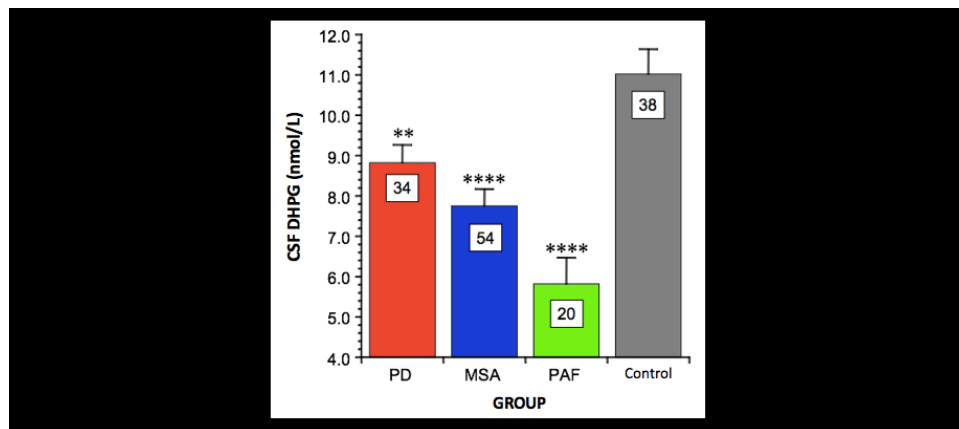
In the setting of NET inhibition, such as due to tricyclic anti-depressants, some amphetamines, or cocaine, for the same amount of NE release there is less reuptake of the released NE. This means that plasma DHPG levels are decreased more than are plasma NE levels. During orthostasis, the increase in plasma NE is larger than the increase in plasma DHPG, and the plasma NE:DHPG ratio is high. This is what is found in postural tachycardia syndrome due to NET deficiency.

The parkinsonian form of multiple system atrophy (MSA-P) can be very difficult to distinguish from Parkinson's disease with orthostatic hypotension (PD+OH). Plasma DHPG can provide a neurochemical clue to the correct diagnosis. This is because sympathetic noradrenergic innervation is generally intact in MSA-P, and the orthostatic hypotension is mainly from baroreflex failure. In PD+OH there is a loss of sympathetic noradrenergic nerves. A low plasma DHPG level

in this setting points to decreased NE stores.

Since DHPG is a deaminated metabolite of NE, MAO inhibition decreases plasma DHPG levels without affecting plasma NE levels. The form of MAO in sympathetic noradrenergic nerves is MAO-A. Even so, treatment with an MAO-B inhibitor can decrease plasma DHPG levels.

CSF DHPG provides a valuable neurochemical means to detect loss of NE stores in the brain. In this regard CSF DHPG is more informative than is CSF NE. The CSF DHPG concentration normally is about 1800 pg/mL, which is more than twice the plasma DHPG level.



CSF DHPG is decreased in PD, MSA, and especially PAF.

CSF DHPG is low in Parkinson's disease (PD) and multiple system atrophy (MSA) and especially low in pure autonomic failure (PAF).

PLASMA AND CSF DOPA

DOPA (3,4-dihydroxyphenylalanine, levodopa) is the immediate product of the rate-limiting enzymatic step in the synthesis of the catecholamines—hydroxylation of tyrosine catalyzed by tyrosine hydroxylase (TH).

Human plasma normally contains a higher concentration of DOPA than of any of the catecholamines. Plasma DOPA is determined complexly, but one determinant is TH activity. Since TH outside the brain is concentrated in sympathetic noradrenergic nerves, patients with severe sympathetic noradrenergic denervation can have decreased plasma DOPA levels. On the other hand, in diseases involving decreased norepinephrine synthesis but normal TH activity, such as Menkes disease, plasma DOPA levels are increased compared to those of DHPG.

Plasma levels of DOPA average about 1,000–2,000 pg/mL. Patients treated with levodopa, such as for Parkinson's disease (PD), can have plasma DOPA levels a thousand times higher than found endogenously.

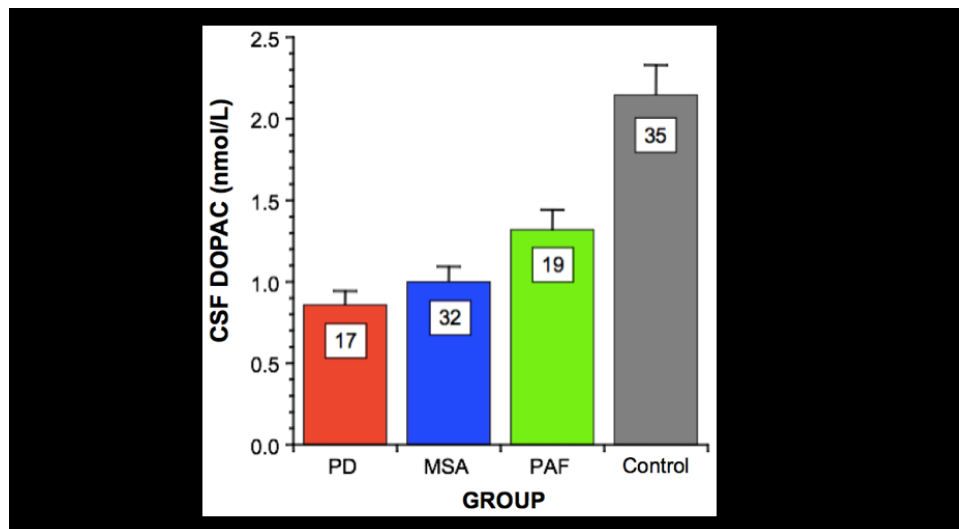
DOPA is normally found in human cerebrospinal fluid (CSF). The concentration is about 700 pg/mL and is lower in levodopa-untreated patients with PD than in healthy controls. Whether low CSF DOPA in PD reflects decreased TH activity in the brain is unknown, however, because the sources and meanings of CSF DOPA have not yet been studied formally.

PLASMA AND CSF DOPAC

DOPAC (3,4-dihydroxyphenylacetic acid) is the main neuronal metabolite of dopamine. Plasma DOPAC levels are much higher than plasma dopamine levels and average about 1,000-2,000 pg/mL.

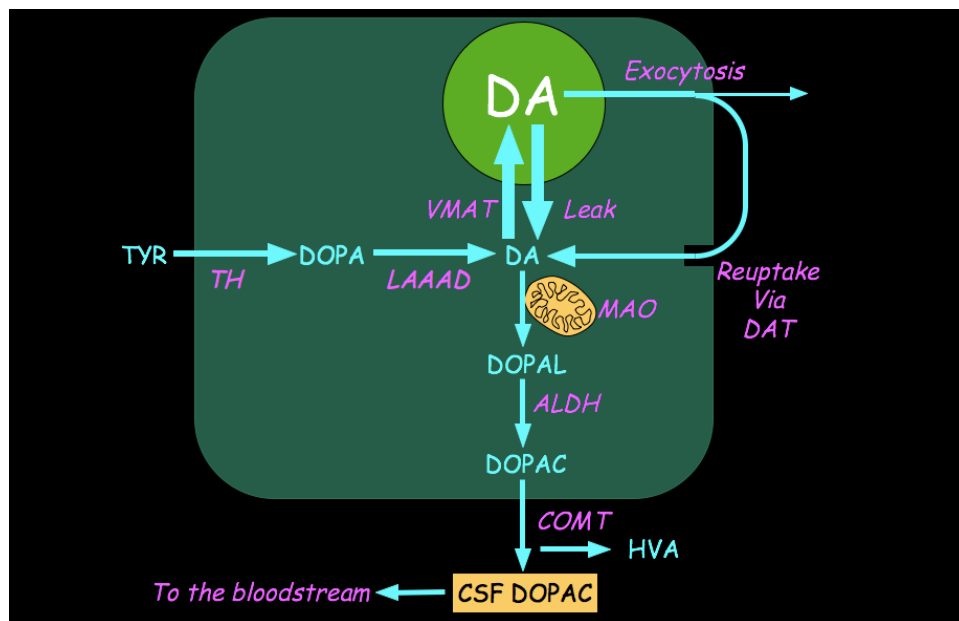
Since DOPAC is a deaminated metabolite, patients on monoamine oxidase inhibitors can have decreased plasma DOPAC levels.

DOPAC levels in cerebrospinal fluid (CSF) provide a neurochemical “window” on the status of dopaminergic innervation in the brain.



CSF levels of DOPAC are low in Parkinson's disease and related disorders.

It seems that in parkinsonism from any cause, CSF DOPAC is decreased.

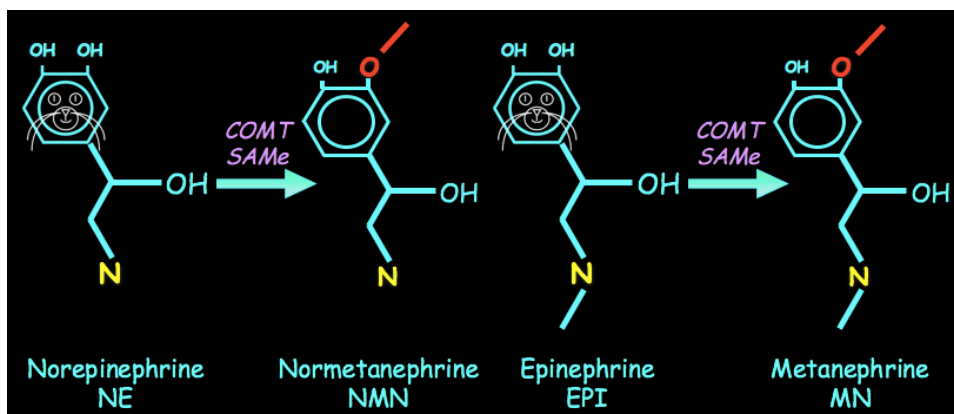


Factors determining CSF DOPAC levels

Low CSF DOPAC can reflect any of several abnormalities. These include a loss of dopaminergic neurons; a vesicular storage defect in the residual dopaminergic neurons or augmented vesicular leakage, as these would deplete dopamine stores and so decrease substrate for monoamine oxidase (MAO) to act on; a decrease in activity of the enzymes MAO, L-aromatic-amino-acid decarboxylase (LAAAD), tyrosine hydroxylase (TH), or aldehyde dehydrogenase (ALDH); an increase in activity of catechol-O-methyltransferase (COMT), which converts DOPAC to homovanillic acid in non-neuronal cells; or increased active secretion of DOPAC, which is an acid, from the CSF space into the bloodstream.

PLASMA METANEPHRINES

In a patient with symptoms or signs suggesting a pheochromocytoma, such as episodic hypertension, sweating, pallor, and headache, the most efficient screening test is measuring plasma levels of free (unconjugated) metanephrines.



COMT catalyzes the conversion of norepinephrine to normetanephrine and of epinephrine to metanephrine.

The term, “metanephrines,” refers to the O-methylated metabolite of norepinephrine, which is normetanephrine (NMN) and the O-methylated metabolite of epinephrine, which is metanephrine (MN).

The enzyme, catechol-O-methyltransferase, or COMT, catalyzes the transfer of a methyl group from the methyl donor, S-adenosyl methionine (SAME) to the catechol nucleus, so that the -OH hydroxyl group is replaced by an -OCH₃ methoxy group.

Unlike the sympathetic nerves, the catecholamine-producing cells in the adrenal medulla express COMT. This means that

under resting conditions norepinephrine (NE) that leaks from the vesicles into the cytoplasm in adrenomedullary cells can be metabolized to normetanephrine (NMN), but NE that leaks from the vesicles into the cytoplasm in sympathetic nerves cannot. Plasma NMN therefore provides a more sensitive, specific test for pheo than does plasma NE. In the case of epinephrine (EPI), there is very little ongoing release of EPI into the bloodstream, whereas there is ongoing release of metanephrine (MN) due to the continuous leakage of EPI from the vesicles into the cytoplasm.

If there were a high rate of sympathetic noradrenergic nerve traffic, plasma NMN could be increased, due to O-methylation of some of the released NE that is taken up by non-neuronal cells. If a patient with hypertension had hyperactivity of the sympathetic noradrenergic system, clonidine administration would drop the rate of sympathetic nerve traffic and decrease plasma NMN levels; but if a patient had a pheo, clonidine administration would fail to decrease plasma NMN.

3-Methoxytyramine is the O-methylated metabolite of dopamine. A high plasma 3-methoxytyramine level is a sensitive test for metastatic pheochromocytoma or paraganglioma. Indeed, plasma 3-methoxytyramine is the most accurate biomarker for discriminating pheo patients with vs. without metastases.

3-Methoxytyramine isn't considered to be a metanephrine, for reasons that escape me.

ANTIBODY TESTS

One mechanism by which autonomic nerves could be harmed is by autoimmunity. The immune system raises an antibody or produces immune cells that target a protein that is expressed in the autonomic nervous system. The autoimmune attack damages or interferes with the function of the nerves.

Probably the most well characterized form of auto-immune attack is autoimmune autonomic neuropathy from a circulating antibody to the neuronal nicotinic receptor. Since ganglionic neurotransmission depends on this receptor, autoimmune autonomic neuropathy can manifest with decreased function of any component of the autonomic nervous system. In autoimmune autonomic ganglionopathy (AAG), the attack is sufficiently severe and generalized to cause all components of the autonomic nervous system to fail clinically—a “pandysautonomia.” In AAG, the titer of the antibody to the neuronal nicotinic receptor correlates with the severity of the patient’s symptoms and signs.

Cancer cells can produce antibodies to proteins expressed by autonomic nerves (“paraneoplastic syndrome”). Anti-Hu antibodies (also known as Type 1 anti-neuronal nuclear antibody, ANNA-1) are especially common in small cell lung cancers.

A variety of infectious diseases can result in autonomic neuropathies, such as mononucleosis, herpes simplex, and Cocksackie B.

Lambert-Eaton myasthenic syndrome is an autoimmune disorder of neuromuscular transmission characterized by antibodies directed against presynaptic, voltage-gated calcium channels, impairing acetylcholine release. This syndrome is most commonly associated with symptoms and signs of parasympathetic nervous system failure.

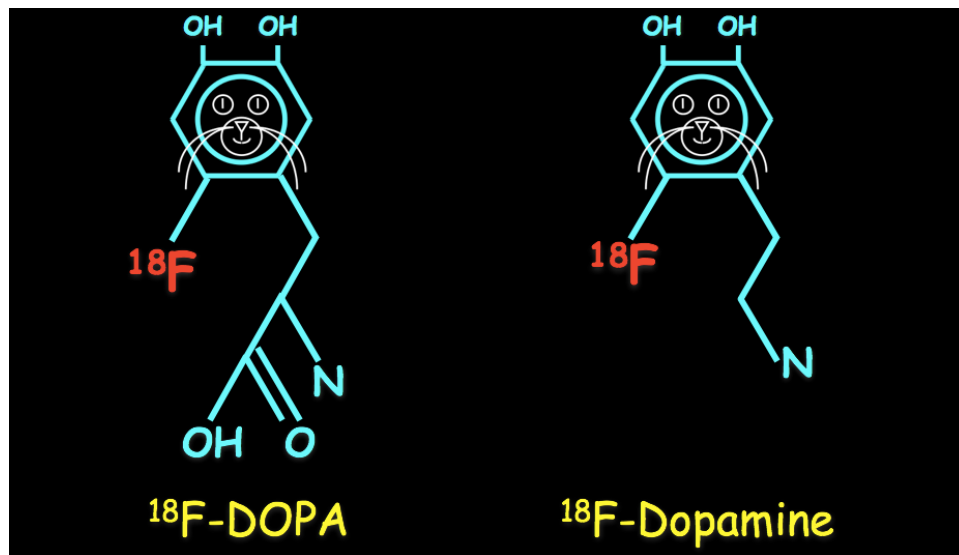
Several diseases can include autonomic neuropathy that may have an autoimmune mechanism, such as diabetes, Guillain-Barré syndrome, Sjogren's syndrome, lupus, and amyloidosis. In general, there is no specific test to identify the specific offending antibody. These are discussed later in this book.

Other antibodies are included in commercially available panels. Some associated with autonomic neuropathies are antinuclear antibody and Rheumatoid factor.

It should be noted that the presence of an antibody, such as to the neuronal nicotinic receptor, does not mean that the antibody is pathogenic and causes or contributes to dysautonomia. It can be very difficult to make this determination with confidence. One way to assess this possibility is by plasma exchange. In this procedure, the patient's blood is drawn into a machine that separates the cells from the plasma, removes the plasma, and infuses the patient's cells back into the patient, along with saline, albumin, and electrolytes. Plasma exchange temporarily decreases circulating levels of all antibodies. Rapid improvement in the patient's symptoms and signs would indicate that one or more antibodies are pathogenic, but it doesn't identify the specific antibody.

Neuroimaging Tests

Neuroimaging is a way to see nervous system tissue. Cardiac sympathetic neuroimaging, to visualize the sympathetic noradrenergic innervation in the heart, can be especially valuable in distinguishing PD with orthostatic hypotension from the parkinsonian form of multiple system atrophy. Cardiac sympathetic neuroimaging can also distinguish Lewy body dementia from Alzheimer's disease. Brain striatal neuroimaging by ^{18}F -DOPA PET scanning is valuable to confirm loss of putamen dopamine terminals, which is a common feature of parkinsonism whether from Parkinson's disease, the parkinsonian form of multiple system atrophy, or progressive supranuclear palsy.



^{18}F -DOPA and ^{18}F -dopamine are catechols.

CARDIAC SYMPATHETIC NEUROIMAGING

Sympathetic nerves to the heart travel with the coronary arteries that deliver blood to the heart muscle. The nerves then dive into the muscle and form mesh-like networks that surround the heart muscle cells. Because neuroimaging tests have a limit of resolution of a few millimeters, the imaging does not show individual nerves but gives a general picture, and since the nerves are found throughout the heart muscle the picture looks very much like a scan of the heart muscle.

The radioactive drugs used for imaging the sympathetic nerves in the heart are given by injection into a vein, and they are delivered to the heart muscle by way of the coronary arteries.

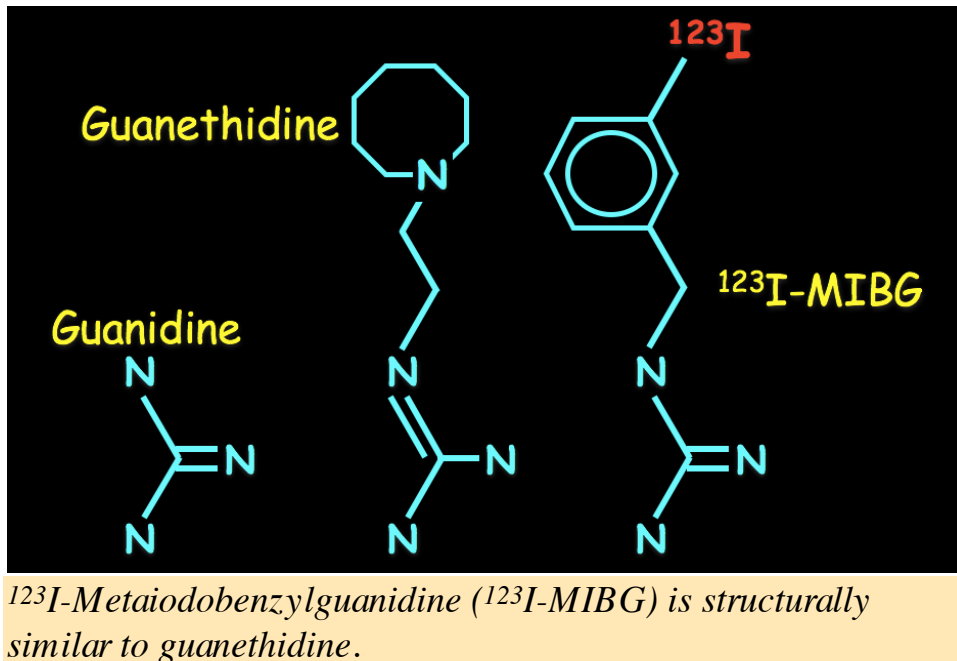
One must be able to distinguish decreased radioactivity in the scan due to loss of sympathetic nerves from decreased radioactivity due to blockage of a coronary artery, because either nerve loss or coronary blockage would lead to the same lack of radioactivity in the heart muscle. Centers that carry out sympathetic neuroimaging therefore may do two scans in the same testing session, one scan to see where the blood is going and the other to see where the sympathetic nerves are.

Cardiac sympathetic neuroimaging is available in few centers in the United States but is done routinely at many centers in Europe and Japan.

MIBG Scanning

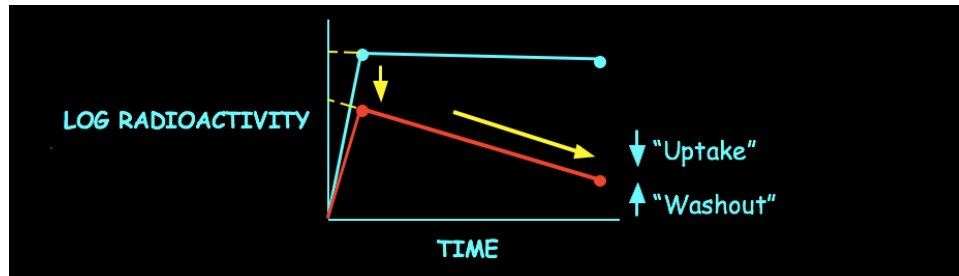
Worldwide the most commonly used sympathetic neuroimaging

agent is ^{123}I -metaiodobenzylguanidine, or ^{123}I -MIBG. ^{123}I -MIBG is a radioactive form of a drug that is taken up by sympathetic nerves, making them visible on a nuclear medicine scanner.



^{123}I -MIBG scanning is used fairly commonly to evaluate possible pheochromocytoma, a tumor that is a rare but important cause of high blood pressure; however, in the United States ^{123}I -MIBG scanning to examine the sympathetic nerve supply to the heart as part of autonomic function testing is still considered to be a research tool.

In common forms of dysautonomia such as postural tachycardia syndrome the problem is not a loss of the sympathetic nerves but a change in activity or function of those nerves. Whether ^{123}I -MIBG scanning can provide information about cardiac sympathetic function is a research question.



The dynamics of radioactivity over time may provide information about the functioning of the sympathetic nerves in the heart.

Fluorodopamine Scanning

In Building 10 of the National Institutes of Health's Clinical Center, our group developed another sympathetic neuroimaging agent, which is 6-[^{18}F]fluorodopamine, or ^{18}F -dopamine. This is a radioactive form of the catecholamine, dopamine.

After injection of ^{18}F -dopamine into a vein, the drug is taken up by sympathetic nerves, and the radioactivity is detected by a special type of scanning procedure called positron emission tomographic scanning, or "PET scanning."

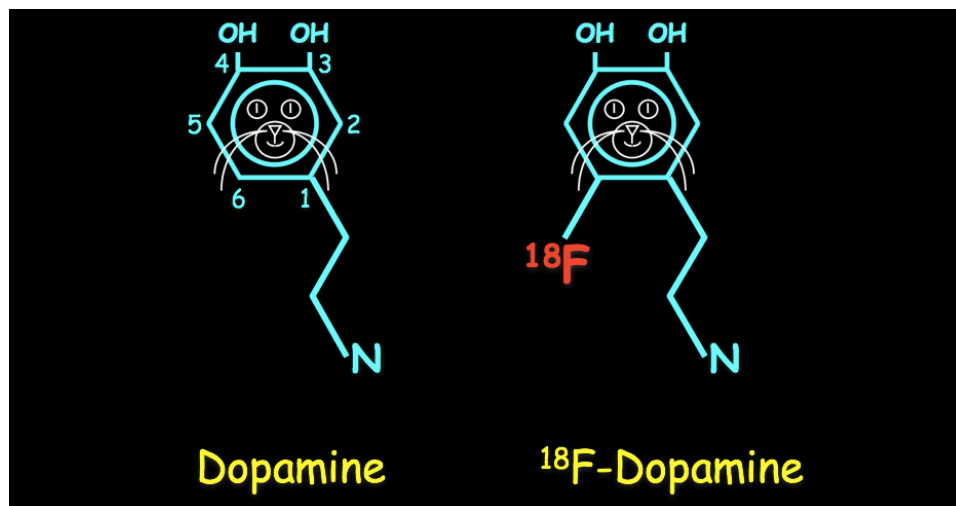
Tomography is a type of scanning based on slices.

Imagine you had a radioactive object in a box. You could determine if there were something radioactive inside by using a detector, such as a Geiger counter. Now suppose you had a large number of little Geiger counters all around the box. Tomographic scans are two-dimensional images, or slices. Tomographic slices would allow you to see what was inside the box at any level. If the object were small, most of the slices

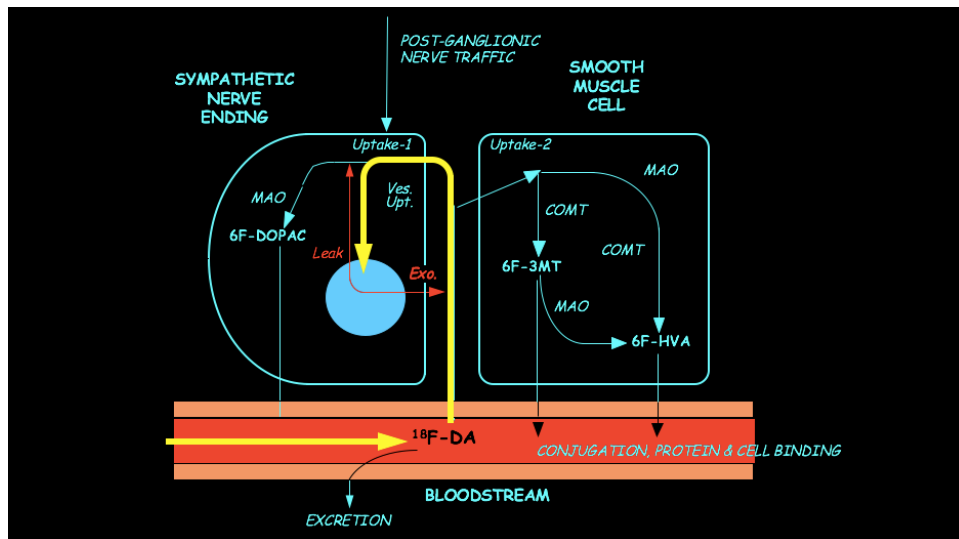
would be empty. Eventually, at the level of the object, you would see an image of the object in the slice.

A positron emitter is a type of radioactive substance that releases a short-lived form of radiation that can penetrate the body and reach detectors outside it, enabling construction of a PET scan. Other tomographic scans in nuclear medicine use a somewhat different source of radioactivity, but the idea is about the same.

Fluorodopamine is structurally similar to two of the biochemicals of the sympathetic nervous system, norepinephrine and adrenaline. Just as some radioactive chemicals get taken up by bone, producing a bone scan, or get taken up by the brain, producing a brain scan, fluorodopamine gets taken up by sympathetic nerves, and the result is a scan of the sympathetic nervous system. For instance, we know that fluorodopamine gets taken up very readily in the heart walls,



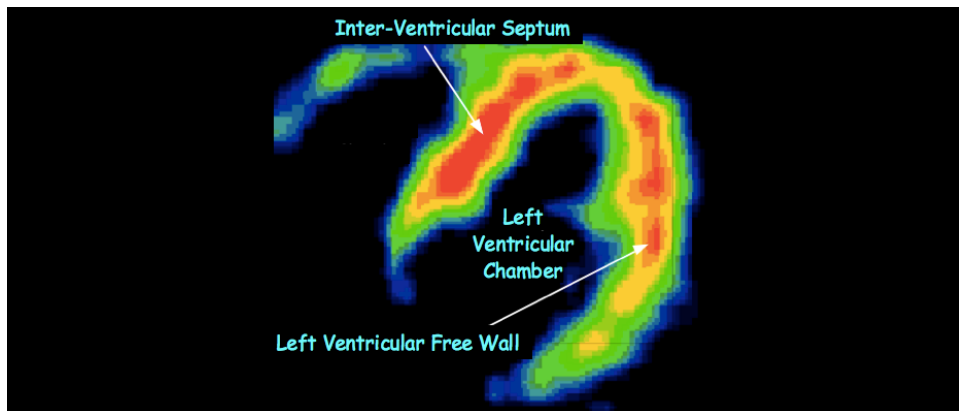
^{18}F -Dopamine is dopamine with a positron-emitting isotope of fluorine, ^{18}F , at the 6 position of the benzene ring.



^{18}F -Dopamine injection leads to radiolabeling of vesicles in sympathetic nerves.

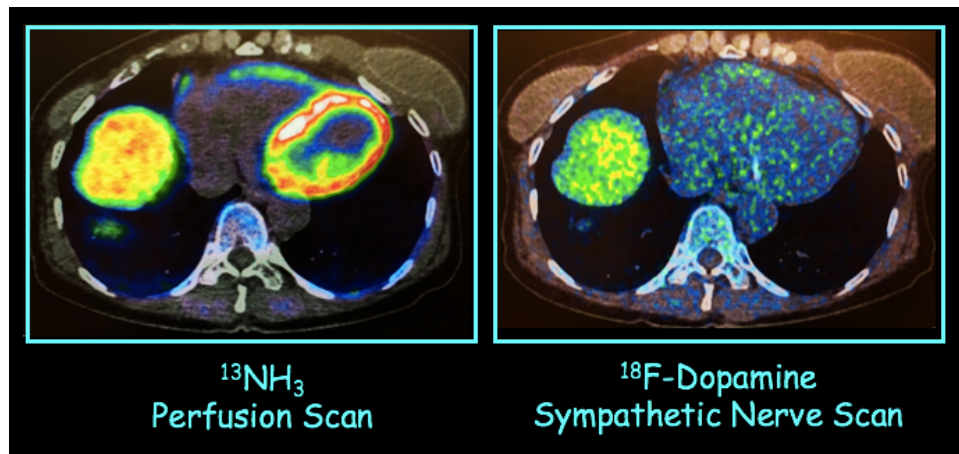
since there are so many sympathetic nerves there.

Because there are so many sympathetic nerves in the heart, PET scans of the heart after injection of fluorodopamine basically look like images of the heart itself.



A normal ^{18}F -dopamine scan showing the sympathetic innervation of the heart.

One can easily make out the main pumping muscle (left ventricular myocardium), the septum between the left and right ventricles, and the left and right ventricular chambers that contain the blood the heart pumps.



^{13}N -Ammonia perfusion and ^{18}F -dopamine sympathetic neuroimaging PET/CT scans in a patient with Parkinson's disease and orthostatic hypotension. The top of the liver is seen well, but the myocardium is not visualized.

Different forms of dysautonomia can produce remarkably different pictures of the sympathetic nerves in the heart by fluorodopamine PET scanning. Probably the most striking pictures occur in diseases where there is a loss of sympathetic nerves, such as in pure autonomic failure and in Parkinson's disease with orthostatic hypotension. Even when the blood flow to the heart muscle is normal, there is no heart muscle visible in the patient's chest!

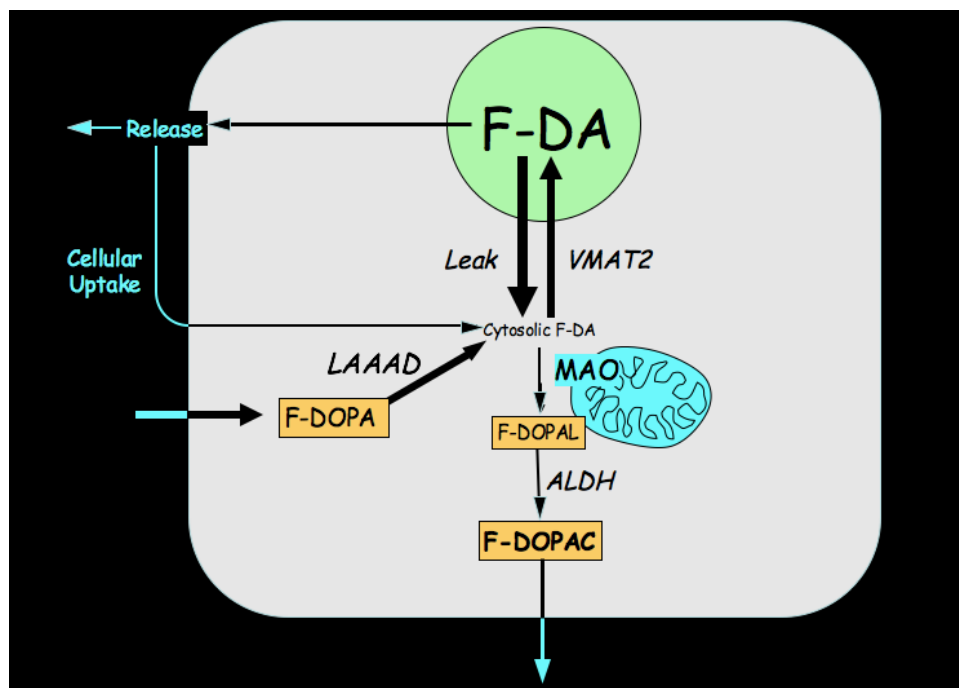
Analysis of the amount of ^{18}F -dopamine-derived radioactivity in the heart over time can provide information about how the sympathetic nerves are functioning. This is a matter of research interest now.

STRIATAL DOPAMINERGIC NEUROIMAGING

^{18}F -Dopamine, which is used for cardiac sympathetic neuroimaging, does not pass through the “blood-brain barrier.” This means that ^{18}F -dopamine PET scanning cannot reveal abnormalities in different structures in the brain. ^{18}F -DOPA, on the other hand, can penetrate the blood-brain barrier.

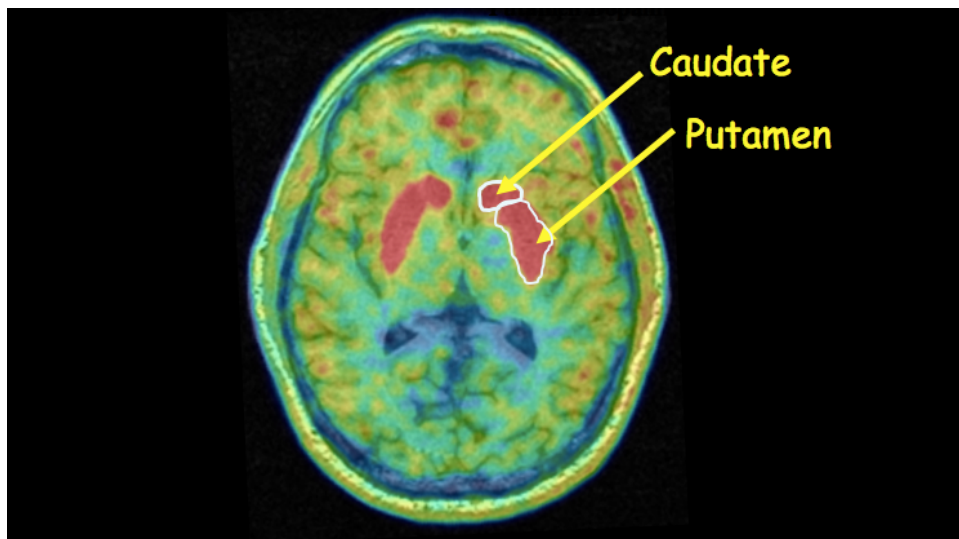
Fluorodopa Scanning

Inside the brain, ^{18}F -DOPA is converted to ^{18}F -dopamine, and the radioactivity is concentrated in regions that store monoamines such as dopamine, norepinephrine, and serotonin.



^{18}F -DOPA striatal neuroimaging is based on conversion of radioactive ^{18}F -DOPA to ^{18}F -dopamine and uptake of the ^{18}F -dopamine into vesicles, making them show up on a PET scan.

The striatum in the brain consists of the caudate and putamen. In a ^{18}F -DOPA PET scan the striata on the two sides of the brain look like slugs, or like a sad clown's eyes. The clown's beady eyes correspond to the head of the caudate. The "eye liner" corresponds to the putamen, which is the major site of damage in Parkinson's disease (PD). As you'll learn later, in PD the eye liner seems washed away.



^{18}F -DOPA PET scan superimposed on the person's MRI scan shows the dopamine-containing terminals in the striatum (caudate and putamen). See the "sad clown's eyes?"

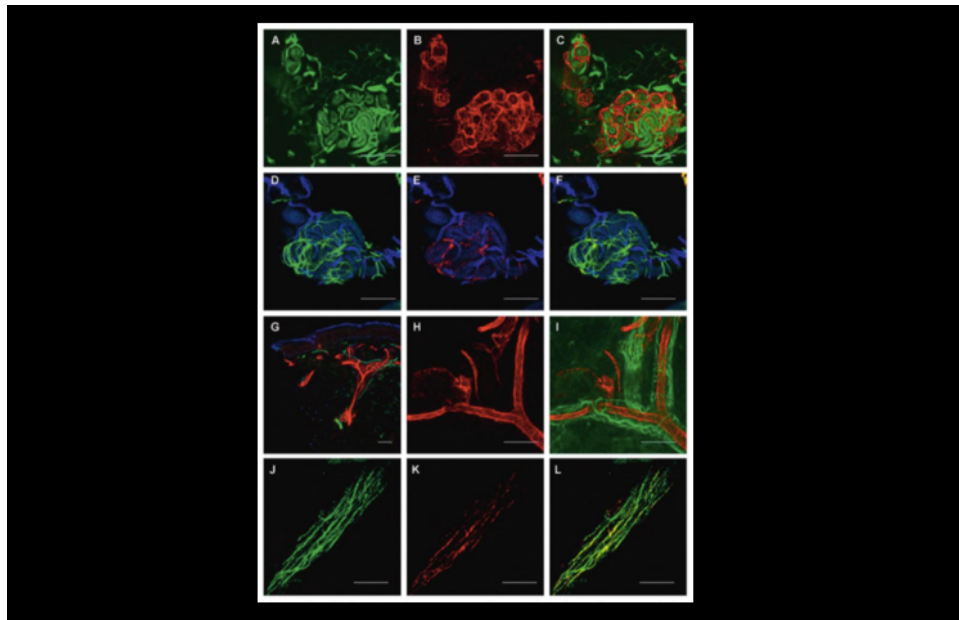
DAT Scanning

There are other imaging agents that can be used like ^{18}F -DOPA to visualize abnormalities of the nigrostriatal dopamine system in the brain. A related type of scan is called a "DAT" scan. DAT stands for the cell membrane dopamine transporter. Since transporters for dopamine are found on the terminals in the striatum, a DAT scan can detect loss of dopamine terminals

such as in Parkinson's disease.

Skin Biopsies

The skin possesses multiple types of nerves. Nerves in the skin that sense touch and vibration are relatively large and conduct impulses quickly. Thin, slow-conducting, non-myelinated nerve fibers in the skin can be identified by a chemical called PGP 9.5. Sympathetic post-ganglionic fibers, whether cholinergic or noradrenergic, and slow-conducting sensory fibers are stained by PGP 9.5.

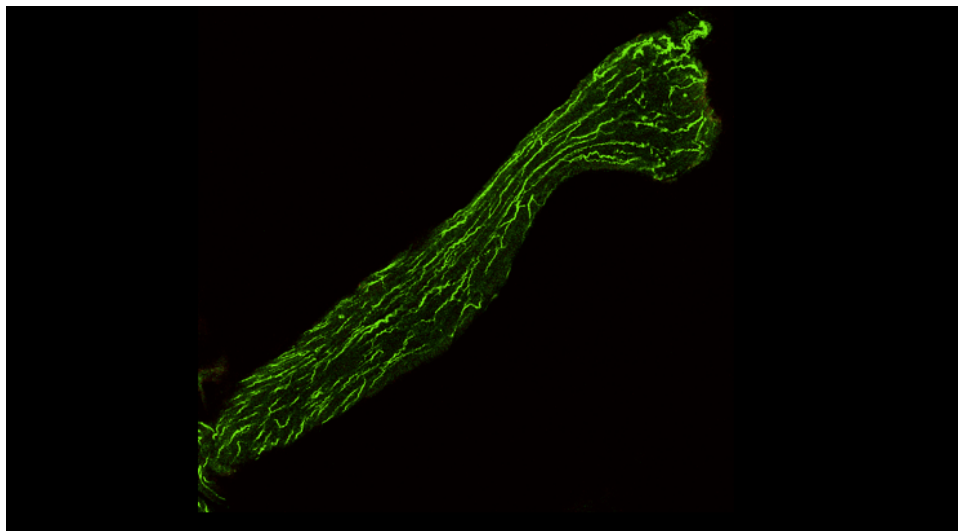


The skin contains several different structures with different types of nerve supplies.

The sweat glands in the skin receive sympathetic cholinergic nerve fibers. These post-ganglionic, non-myelinated, slow-conducting fibers release acetylcholine. The acetylcholine

binds to muscarinic receptors, evoking sweat secretion. In skin biopsy samples, one can identify the sympathetic cholinergic fibers by their contents of vasoactive intestinal peptide (VIP) or choline acetyltransferase (ChAT).

The hair follicles have small muscles attached to them called pilomotor or *arrector pili* muscles. The pilomotor muscles are responsible for the hair standing up, or piloerection, when you are exposed to cold or when you are emotionally distressed. The muscles receive sympathetic noradrenergic nerve fibers. These are post-ganglionic, non-myelinated, slow-conducting fibers that release norepinephrine. The norepinephrine binds to alpha-adrenoceptors, and the hair stands up. In skin biopsy samples, one can identify the sympathetic noradrenergic fibers by their contents of dopamine-beta-hydroxylase (DBH) or tyrosine hydroxylase (TH).



Sympathetic nerves revealed by tyrosine hydroxylase immunofluorescence microscopy in arrector pili muscle.

Usually skin biopsy samples contain tiny blood vessels. The

walls of arterioles receive sympathetic noradrenergic nerve fibers, which can be identified by PGP 9.5, DBH, or TH staining.

The *arrector pili* muscles and the walls of arterioles receive purely sympathetic noradrenergic innervation. PGP 9.5 staining thereby can identify sympathetic noradrenergic nerves specifically by the signal in these structures.

Genetic Tests

Most forms of dysautonomia do not run in families, but some do. Knowledge about inherited predispositions to dysautonomias is expanding rapidly.

To understand genetic causes of these diseases you have to know what a mutation is.

A mutation is like a typo in the genetic encyclopedia.

The encyclopedia consists of two sets of 23 volumes (chromosomes) each. The last two volumes are the same size in girls (each volume is X), whereas the last two differ in size in boys (the larger volume X, the smaller Y).

In autosomal dominantly transmitted diseases, even one copy of the mutated gene is sufficient to produce the disease. One-half the family members will inherit the mutation and have the disease (assuming perfect “penetrance”).

In autosomal recessive diseases, both parents have the mutated gene on one of their chromosomes. They are carriers. Since each parent donates one chromosome, the chances are 50% that they will donate the chromosome carrying the mutation, and the chances are 25% that their offspring will carry the mutation on both chromosomes and have the disease.

In X-linked recessive diseases involving a mutation on the X chromosome, the disease is expressed in boys but not in girls, because the other X chromosome does not carry the mutation. The mothers of boys with an X-linked recessive inherited disease are carriers, because the affected X-chromosome is coming from the mothers. If a known carrier is pregnant with a boy, the chances are 50% that he will have the disease and 50% that he won't—and neither will any of his descendants.

FAMILIAL DYSAUTONOMIA

The most well known inherited dysautonomia is familial dysautonomia (FD), or Riley-Day syndrome. FD runs in families of Ashkenazi extraction. The cause is a mutation of the gene, IKBKAP. Genetic screening for FD is now available.

DBH DEFICIENCY

A very rare cause of orthostatic hypotension is deficiency of the enzyme, dopamine-beta-hydroxylase (DBH). This enzyme is required to produce norepinephrine. Genetic testing may be indicated in patients with orthostatic hypotension who have biochemical test results that are consistent with DBH deficiency.

NET DEFICIENCY

A very rare cause of postural tachycardia syndrome (POTS) is mutation of the gene for the cell membrane norepinephrine transporter (NET). Although POTS is relatively common, POTS from this genetic cause is extremely rare. Genetic screening for NET deficiency may be indicated for POTS patients who have biochemical or neuroimaging test results that are consistent with NET deficiency.

MENKES DISEASE

Menkes disease is a rare disease of copper metabolism. Because dopamine-beta-hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine, is a copper enzyme, Menkes disease involves a form of dysautonomia due to decreased norepinephrine production.

Genetic mutation of a copper ATPase causes Menkes disease. The gene is located on the X-chromosome. This means that Menkes disease is transmitted as an X-linked recessive trait. The patients are virtually always boys, since males have only 1 X chromosome. The mother, with 2 X chromosomes, is a carrier. If a woman has given birth to a baby with Menkes disease, then chances are 50:50 that if she has another son the baby will be affected. Genetic testing for the mutated gene can be done in the fetus, but as discussed later the most efficient test to diagnose Menkes disease in at-risk newborns is measuring plasma levels of catechols.

PARKINSON'S DISEASE

Occasionally Parkinson's disease (PD) runs in families. The first identified genetic cause of familial PD was mutation of the gene encoding the protein, alpha-synuclein, in 1997. The discovery was in Greek-Italian-American kindred in which PD was transmitted as an autosomal dominant trait. In other words, half the family members had PD. Subsequently it was found in another family that PD can result from replication of a normal alpha-synuclein gene. More recently it has been found that people who carry the mutation that produces Gaucher disease are at increased risk of developing PD. Ashkenazim and North African Arabs with familial PD often carry a mutation of the gene encoding a protein called LRRK2. In the United States, however, the frequencies of all these genetic abnormalities are low.

In general, the more common the genetic alteration in the population, the lower the risk associated with that alteration. In my experience so far, analyses for the above genes have been negative even in patients with a family history of PD.

Which Tests are Done Where?

Few hospitals in the United States carry out comprehensive autonomic function testing.

Physiological tests such as measurements of heart rate

responses to the Valsalva maneuver are readily available, beat-to-beat blood pressure responses to the maneuver and the QSART and skin biopsies are done in several specialized autonomic function testing centers, neurochemical tests such as plasma norepinephrine and adrenaline levels are done in fewer centers, and as of this writing neuroimaging tests are rarely available in the United States, because third party payers don't cover them. At this point there are only a few genetic tests for particular forms of dysautonomia, such as familial dysautonomia.

At a minimum the battery of autonomic function tests at a given medical center should be able to identify abnormalities of regulation of the circulation by the sympathetic noradrenergic system, sweating by the sympathetic cholinergic system, and heart rate by the parasympathetic nervous system.

Other types of indicated autonomic testing would depend on the particular problem the patient is facing. For instance, for complete assessment of dysautonomia in a patient with evidence of a neurodegenerative disease such as Parkinson's disease, neuroimaging should be available to examine dopamine centers in the brain and the supply of sympathetic nerves in the heart; while for assessment of postural tachycardia syndrome, measurement of blood volume and the status of the renin-angiotensin-aldosterone system may be indicated.

As part of tilt table testing for the evaluation of autonomically mediated syncope, I think it is important to track plasma adrenaline and norepinephrine levels. This is the only way to detect differential changes in activities of the sympathetic adrenergic and sympathetic noradrenergic systems—

sympathoadrenal imbalance—which seems to be a key factor in fainting reactions.

There is now an autonomic Rare Diseases Clinical Research Consortium. The founding centers in the Consortium are Vanderbilt University School of Medicine in Nashville, TN; the Mayo Clinic in Rochester, MN; the New England Deaconess Medical Center in Boston, MA; the NYU Medical Center in New York City, NY; and the National Institute of Neurological Disorders and Stroke in Bethesda, MD. These centers routinely carry out autonomic function testing as part of their research under the Consortium.

There is also a newly inaugurated certification program in autonomic disorders, under the United Council of Neurological Subspecialties (UCNS). Physicians who are certified under the program are knowledgeable about autonomic function testing.

STARS IN THE DYSAUTONOMIAS UNIVERSE

In this part you will learn about several examples of dysautonomias.

The approach is not encyclopedic. Please bear in mind that the descriptions here are not meant to be exhaustive, and individual patients can have symptoms that overlap across several disorders.

The presentation generally follows the sequence in the “dysautonomias universe,” beginning with pediatric, then adult, then geriatric conditions. Within each domain the more common conditions come first.

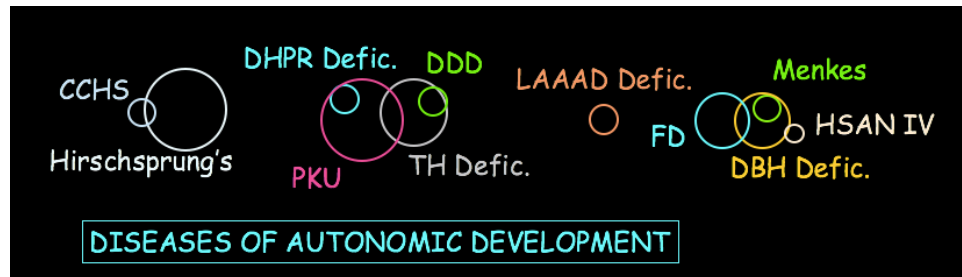
Although for teaching purposes emphasis is placed on diseases that are known or suspected to involve a primary abnormality of the autonomic nervous system, most dysautonomias in general medical practice reflect harm because of worsening of an independent pathologic state, secondary consequences of another disease, or effects of a drug or other treatment.

Recall the definition of dysautonomia as a condition in which altered function of one or more components of the autonomic nervous system adversely affects health. The old man who has a heart attack while shoveling snow provides an example of damage because of an interaction with an independent pathologic state—coronary artery disease. Common, chronic disorders such as diabetes, heart failure, kidney failure, and neurodegenerative diseases are all associated with

dysautonomias of one kind or another. Drugs and other treatments for any of a variety of problems, from hypertension to benign prostatic hypertrophy to cancer to the common cold, can cause harm by stimulating or inhibiting parts of the autonomic nervous system.

INHERITED OR CONGENITAL DYSAUTONOMIAS

Several inherited or congenital diseases have been described that feature a form of dysautonomia. The following discussion describes a few of them. Most are severe and become manifest in infancy or childhood.



Several forms of dysautonomia in children involve abnormal development of parts of the autonomic nervous system.

Inherited forms of dysautonomia are rare but can be severe or lethal.


HSANs

HSAN stands for hereditary sensory and autonomic neuropathy. This is a family of inherited conditions that all feature decreased ability to sense pain. Because of the sensory loss, the

patients can self-mutilate. All forms of HSAN are rare. The most common is familial dysautonomia (HSAN III), followed by congenital insensitivity to pain with anhidrosis (CIPA), which is HSAN IV.

FAMILIAL DYSAUTONOMIA (HSAN III)

The prototype of an inherited dysautonomia is familial dysautonomia (FD), also known as Riley-Day syndrome and hereditary sensory and autonomic neuropathy type III (HSAN III). FD is a rare inherited disease that features abnormalities in sensation and in functions of the autonomic nervous system. FD runs in families of Ashkenazi extraction.



"Crises"
(vomiting, sweating, agitation, variable BP)

Kyphoscoliosis

Corneal lesions

Aspiration & GERD (Nissen fundoplication)

Burns, corneal lesions, Charcot joints

Oro-dental self-mutilation

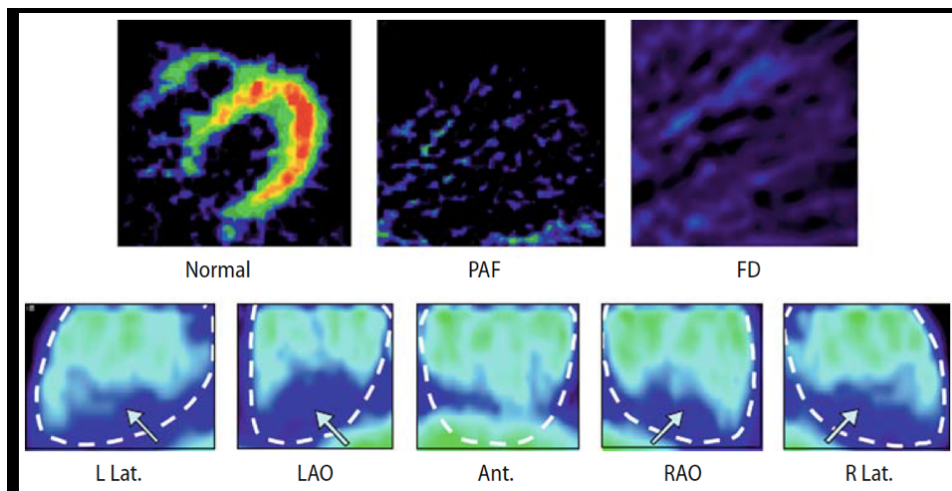
Neurogenic orthostatic hypotension

Some complications of familial dysautonomia.

The cause of FD is a mutation of the gene, *IKBKAP*. The mutation results in decreased levels of the protein, IkappaB kinase-associated protein (IKAP), especially in nervous system tissue. The functions of IKAP remain unknown, but it may have something to do with the development of small nerve

fibers, such as non-myelinated sensory fibers and post-ganglionic sympathetic noradrenergic nerves. With supportive treatment, the outlook for FD patients has improved greatly over recent years; many patients are over 20 years old.

Children with FD have a few signs that are diagnostic, including lack of overflow tears, lack of lingual fungiform papillae, and absence of a histamine flare reaction. Adult FD patients typically have orthostatic hypotension, associated with subnormal increments in plasma levels of the sympathetic neurotransmitter, norepinephrine, when the patient stands up.

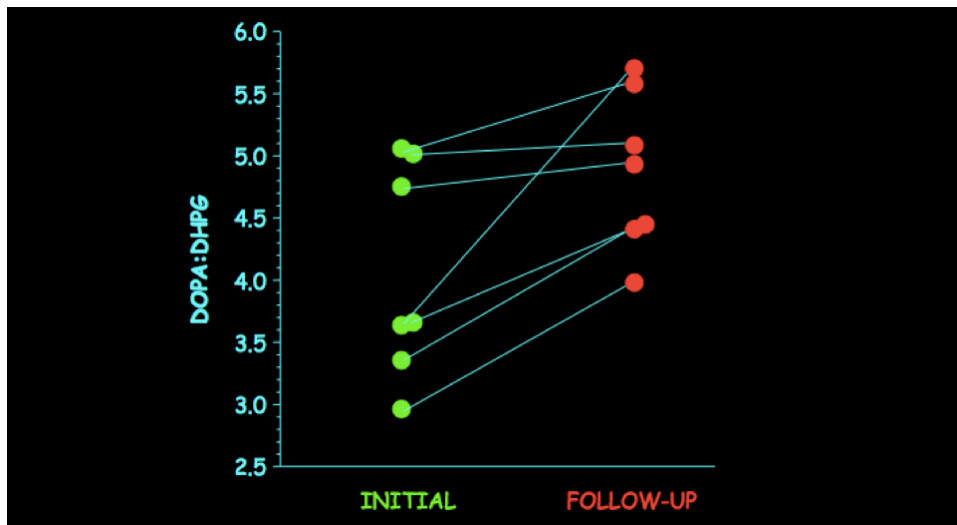


Familial dysautonomia involves decreased cardiac noradrenergic innervation in the more distal regions of the heart.

FD patients are prone to crises of vomiting, sweating, fast heart rate, and high blood pressure. The crises can be life-threatening. The patients often have severe orthopedic problems. Because of inability to sense heat, the patients are at high risk of burns of the mouth or esophagus due to drinking scalding hot liquid.

With genetic screening tests, FD can be detected in utero.

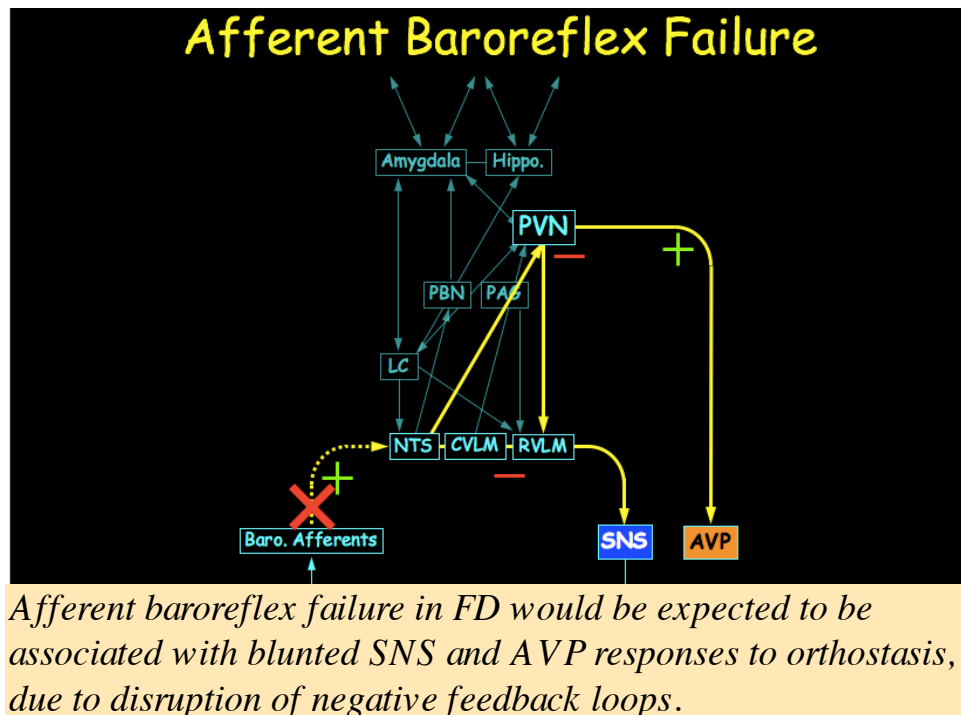
FD seems to involve incomplete development of sympathetic noradrenergic nerves.



There is evidence for progressive neurodegeneration of sympathetic noradrenergic neurons in FD.

Adult FD patients have neuroimaging evidence for decreased cardiac sympathetic innervation, especially in the left ventricular free wall. The ratio of DOPA: DHPG in plasma is increased in all FD patients, probably reflecting decreased norepinephrine synthesis. Over the course of the disease there is evidence for progression of the sympathetic noradrenergic denervation, as plasma DOPA: DHPG ratios increase.

Blood pressure lability in FD patients has been attributed to baroreflex failure, due to decreased information coming to the



brain from baroreceptors—an afferent lesion. This would fit generally with the concept of a hereditary sensory and autonomic neuropathy. Consistent with an afferent lesion, FD patients have attenuated responses of both plasma NE and AVP levels during orthostasis.

CONGENITAL INSENSITIVITY TO PAIN WITH ANHIDROSIS (CIPA, HSAN IV)

In congenital insensitivity to pain with anhidrosis (HSAN IV), patients often have self-mutilation.

HSAN IV can be caused by mutation of the gene encoding neurotrophic tyrosine kinase receptor type 1 (NTRK1).

Self-Mutilation in HSAN IV



Self-mutilation in HSAN IV reflects lack of pain sensation.

NTRK1 is a receptor that normally is phosphorylated in response to nerve growth factor (NGF). Because of the lack of phosphorylation, there is a deficiency in the neurotrophin signaling pathway that is responsible for the development and maintenance of autonomic and sensory fibers.

As one might predict, in HSAN IV plasma levels of norepinephrine (NE) are extremely low and fail to increase during orthostasis. Blood pressure responses can be only mildly affected, possibly because of denervation supersensitivity. Heart rate responses to head-up tilting are normal in HSAN IV, which makes sense in that NGF is not thought to be required for parasympathetic nervous system (PNS) development or functioning. The associated finding of normal plasma epinephrine (EPI) levels in HSAN IV is consistent with pathways separate from NGF participating in development and functioning of the sympathetic adrenergic system (SAS).

Congenital Central Hypoventilation Syndrome (CCHS)

Congenital central hypoventilation syndrome (CCHS) used to be called “Ondine’s curse.”

According to a French/German myth, the sea nymph Ondine (“unda” is Latin for “wave”) falls in love with and marries a mortal. He promises her his every waking breath but commits adultery. As punishment he is cursed by not being able to carry out automatic bodily functions without conscious effort. If he ever fell asleep he would stop breathing and die, and that’s what happens.



Artists’ depictions of Ondine (Undine)

The main manifestation of CCHS is apnea (cessation of breathing) during sleep. The patients breathe normally while awake but hypoventilate during sleep. The drop in oxygen and buildup in carbon dioxide do not stimulate ventilation.

In most cases of CCHS the causative gene is in the pairedlike

homeobox gene (PHOX2B), and mutation in the PHOX2B gene is now required to diagnose CCHS. Normally, the PHOX2B gene contains a 20-alanine coding repeat region. An increased number of polyalanine repeats in this region is referred to as polyalanine repeat expansion mutation (PARM). Over 90% of patients with CCHS carry a PARM in the PHOX2B gene. The remaining 10% have nonpolyalanine repeat mutations, such as from missense, nonsense, or frameshift mutations.

The protein encoded by the PHOX2B gene is a transcription factor responsible for regulating expression of genes involved with development of the autonomic nervous system, including dopamine- β -hydroxylase (DBH), which is required for norepinephrine (NE) synthesis. Phox2B is expressed in brainstem centers involved in regulation of autonomic outflows and ventilation, such as the retrotrapezoid nucleus (RTN). The RTN plays a key role in ventilatory responses to carbon dioxide buildup (hypercarbia) or decreased pH. CCHS also seems to involve loss of neurons in the locus ceruleus, the main source of NE in the brain and an important center for arousal and vigilance.

CCHS is associated commonly—but not always—with manifestations of autonomic failure, including pupillary abnormalities, hypothermia, decreased sweating, decreased heart rate variability, episodes of sinus arrest, and Hirschsprung's disease.

CCHS is associated with poor cognitive development, attributed at least partly to prolonged bouts of cerebral hypoxia. CCHS can now be diagnosed early in neonatal life, enabling institution of artificial ventilation. CCHS patients can now

living well into adulthood with much improved neurocognitive outcome.

Diseases of Catecholamine Synthesis

PKU

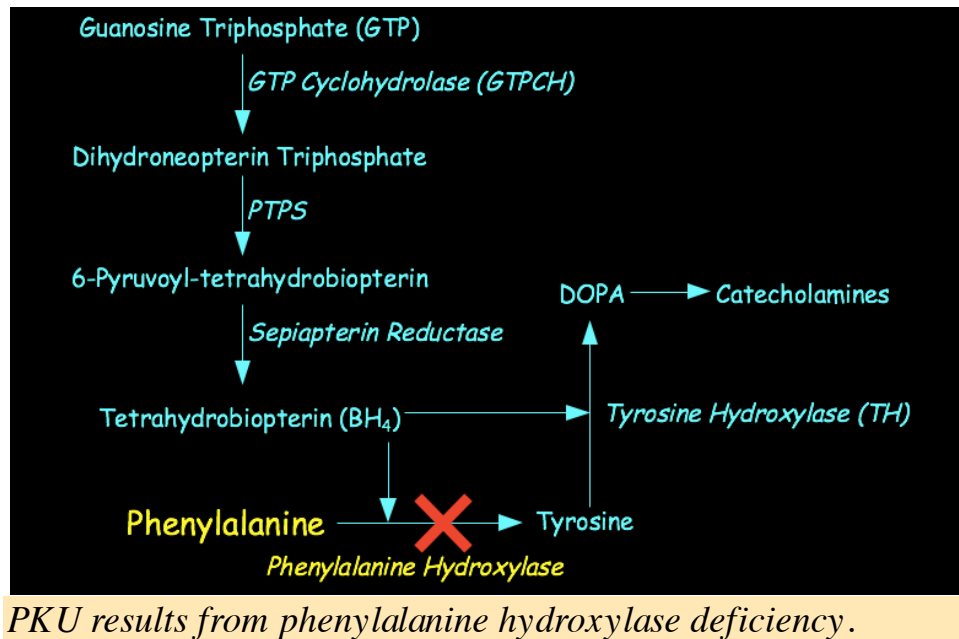
If you have read the label on a can of diet soda that contains the sweetener, aspartame, you have seen a warning for people with a disease called phenylketonuria (PKU).

People with classic PKU have a deficiency of phenylalanine hydroxylase, the enzyme that converts the amino acid phenylalanine to tyrosine. Due to this deficiency, ingesting foods rich in phenylalanine can lead to a buildup of phenylalanine; too much phenylalanine is toxic, especially in infants and children.

Aspartame is broken down to phenylalanine in the body, and so drinking the diet soda pop might cause damage.

For phenylalanine hydroxylase to work requires a co-factor called tetrahydrobiopterin (BH_4). BH_4 is also a required co-factor for tyrosine hydroxylase (TH), so that BH_4 is required for synthesizing catecholamines in the body. BH_4 is also a co-factor for the synthesis of serotonin and nitric oxide.

In dihydropteridine reductase deficiency there is an inability to recycle BH_4 . This causes an atypical form of PKU in which even restricting phenylalanine does not protect the infant from

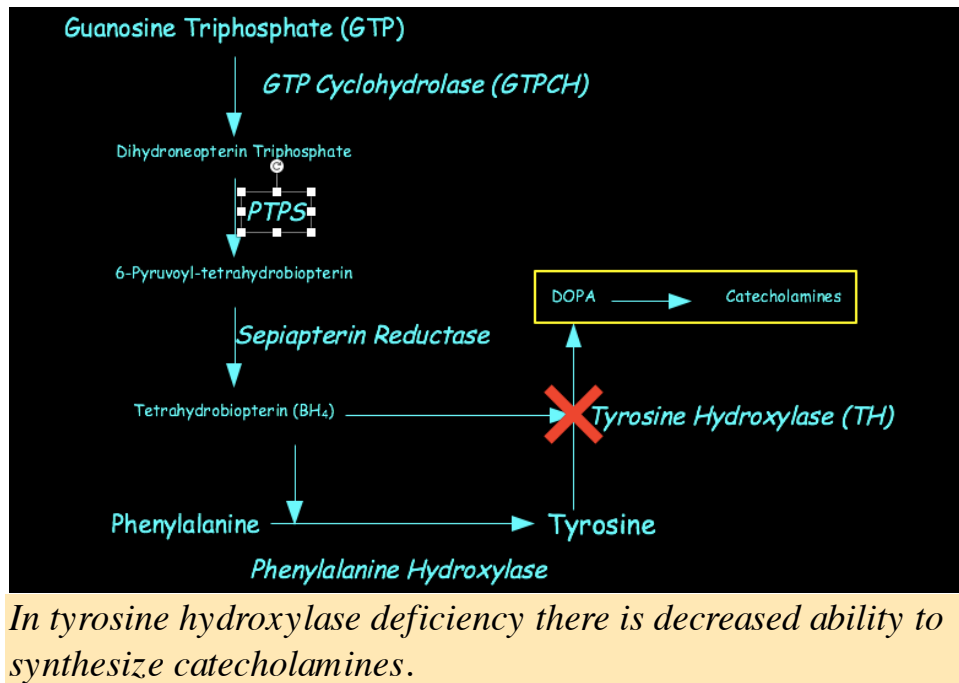


developing a neurodegenerative disease, and death occurs in childhood.

TH Deficiency

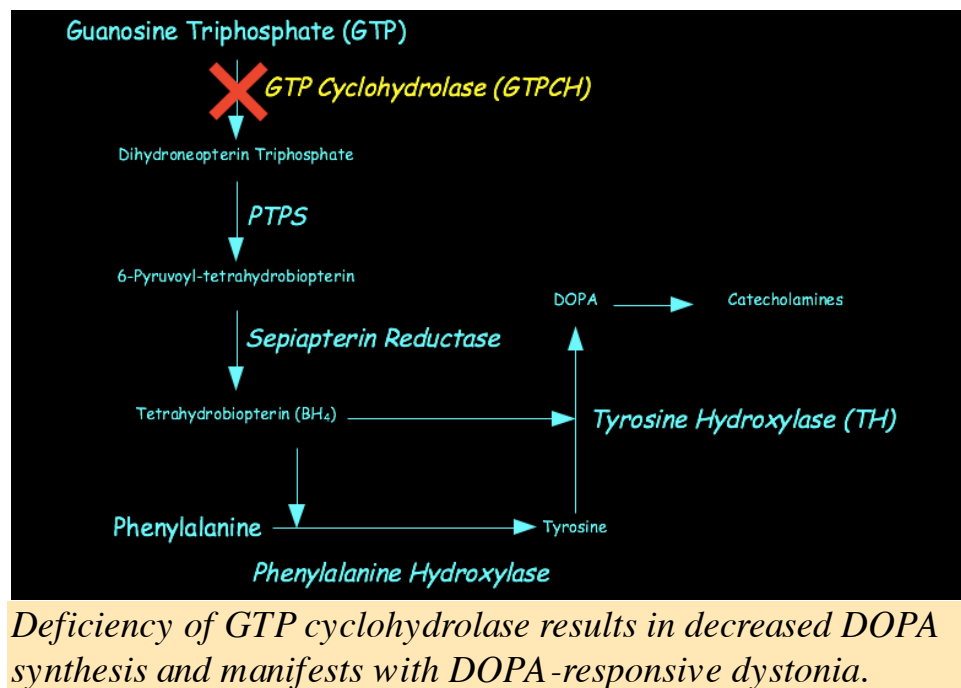
Tyrosine hydroxylase (TH) is the rate-limiting enzyme in the biosynthesis of the catecholamines dopamine, norepinephrine, and epinephrine.

TH deficiency is a rare genetic disorder transmitted as an autosomal recessive trait. The deficiency results in a wide spectrum of abnormalities, from a mild parkinsonian movement disorder developing during childhood to a life-threatening neurological disorder in infancy. As for Segawa's disease (discussed in the next section), patients with TH deficiency respond to levodopa treatment.



DOPA-Responsive Dystonia

GTP cyclohydrolase (GTPCH) is the first enzyme in the synthetic cascade leading to tetrahydrobiopterin (BH₄). Since BH₄ is a co-factor for tyrosine hydroxylase (TH), GTPCH deficiency manifests as a form of parkinsonism with dystonia, called DOPA-responsive dystonia (also called Segawa's disease). The symptoms get worse as the day goes on. Autosomal-dominant DRD comes from mutation of the GTPCH gene. Autosomal-recessive forms of the disease come from mutations of the genes encoding sepiapterin reductase or TH. The disease usually manifests in childhood.

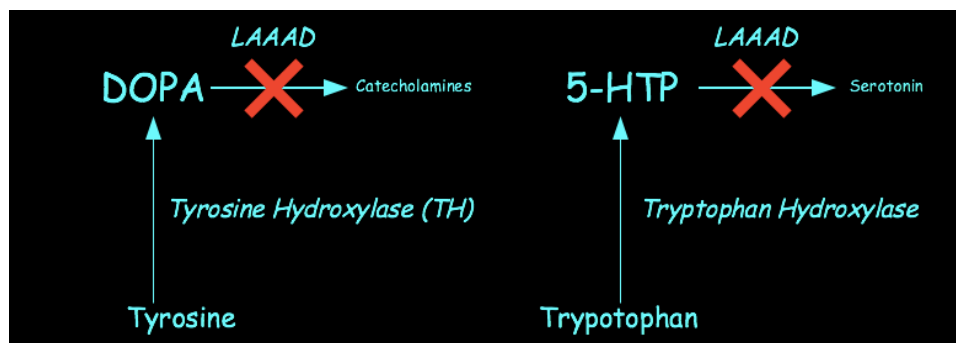


LAAAD Deficiency

L-aromatic-amino-acid decarboxylase (LAAAD, AADC, also called DOPA decarboxylase) catalyzes the conversion of DOPA to the catecholamines and 5-hydroxytryptophan to serotonin (5-hydroxytryptamine). LAAAD uses pyridoxal phosphate (vitamin B6) as a co-factor.

LAAAD deficiency presents as a severe neurological disease in the first year of life. The disease is transmitted as an autosomal recessive trait. The affected infant feeds poorly, startles easily, has disturbed sleep, and experiences episodes of abnormal rotation of the eyeballs (oculogyric crises), irritability, muscle spasms, and involuntary movements.

Because of the inability to synthesize norepinephrine and epinephrine, the patients have low blood pressure (hypotension), a tendency to low blood sugar (hypoglycemia), droopy eyelids (ptosis), nasal congestion, and poor regulation of core temperature. Due to unopposed parasympathetic nervous system influences, the pupils are constricted (miosis), and often there is gastroesophageal reflux.



Deficiency of L-aromatic-amino-acid decarboxylase (LAAAD) causes deficiency of catecholamines and serotonin.

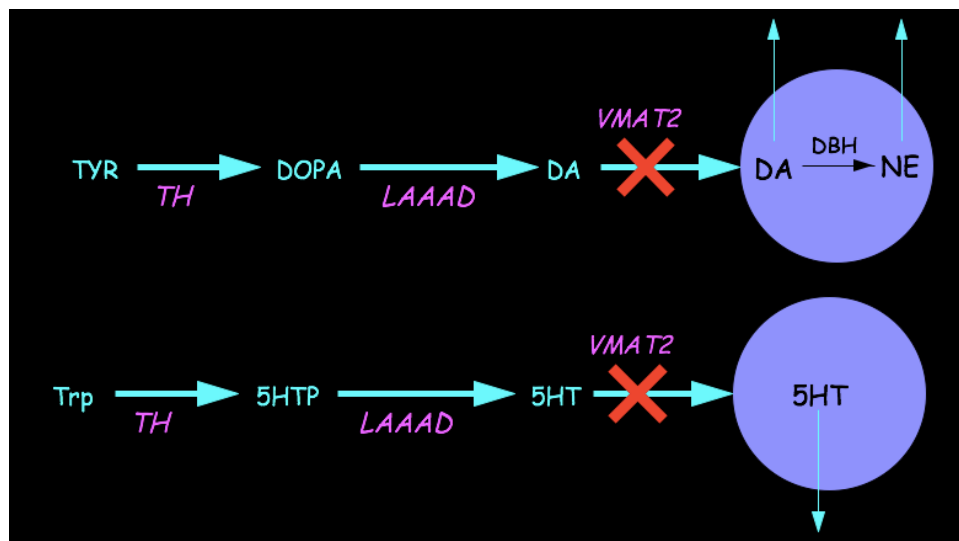
Patients with LAAAD deficiency have a characteristic neurochemical pattern, with high DOPA and 5-hydroxytryptophan levels and low levels of catecholamines, catecholamine metabolites, serotonin, and 5-hydroxyindoleacetic acid (5-HIAA).

Treatment with levodopa, 5-hydroxytryptophan, dopamine receptor agonists, serotonin receptor agonists, and cholinergic receptor antagonists may be tried. It has been proposed that the patients might benefit from a form of gene therapy based on an adeno-associated virus to increase LAAAD activity.

VMAT2 Deficiency

The type 2 vesicular monoamine transporter (VMAT2) transports the monoamines dopamine (DA), norepinephrine (NE), epinephrine (EPI), and serotonin (5-HT) into storage vesicles. Release of these chemical messengers occurs by exocytosis of the contents of the vesicles. Interference with VMAT2 causes dysfunction of all the monoaminergic systems.

Mutation of the gene encoding VMAT2 produces a severe, lethal pediatric disease. Among several manifestations of congenital VMAT2 deficiency, one is parkinsonism.



The monoamines dopamine (DA), norepinephrine (NE), and serotonin (5HT) are stored in and released from vesicles. VMAT2 deficiency interferes with the functions of all three monoaminergic systems.

In mice, knocking out the VMAT2 gene is incompatible with

life. A mouse strain has been created with about a 90% decrease in VMAT2 activity.

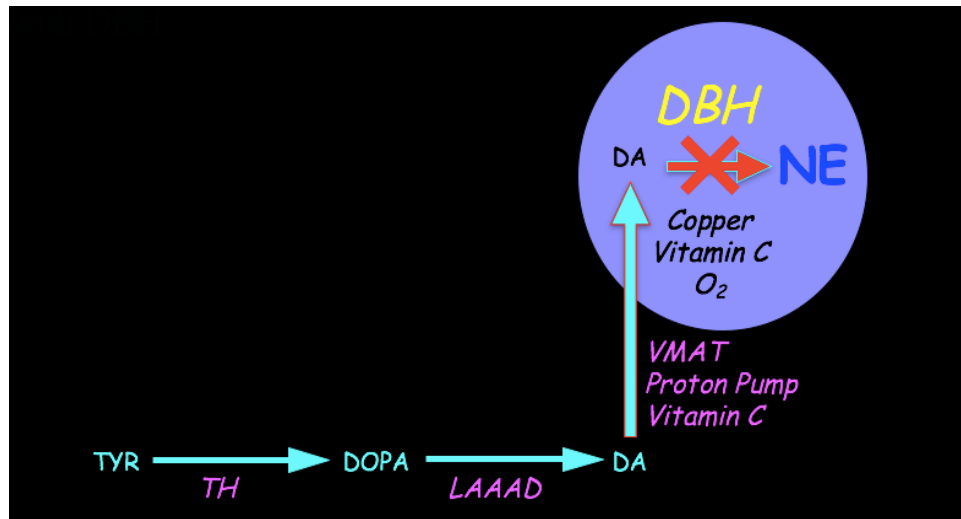
This strain develops aging-related movement abnormalities resembling those in Parkinson's disease. Conversely, mice that over-express VMAT2 are relatively resistant to manipulations that produce parkinsonism. One hypothesized explanation for why VMAT2 deficiency in mice produces aging-related parkinsonism is that the DA synthesized in the neuronal cytoplasm cannot be taken up into vesicles and instead undergoes spontaneous and enzyme-catalyzed oxidation; the oxidation products are toxic and may destroy the neuron.

DBH Deficiency

The enzyme, dopamine-beta-hydroxylase (DBH), is required for production of norepinephrine in the body. Patients with DBH deficiency have orthostatic hypotension and very low plasma norepinephrine levels, even though the post-ganglionic sympathetic innervation of the heart and blood vessels is present.

Sympathetic cholinergic system function is intact in patients with DBH deficiency. The patients have normal sweating, even though they have sympathetic neurocirculatory failure.

Treatment with L-dihydroxyphenylserine (L-DOPS) bypasses the enzyme deficiency and results in remarkable improvement that is virtually curative in DBH deficiency.



Patients with DBH deficiency have decreased synthesis of norepinephrine.

Mice with knockout of the DBH gene do not survive to birth. How it is that people with DBH deficiency survive and, with norepinephrine precursor treatment, thrive remains a medical scientific mystery.

Menkes Disease

Menkes disease, also known as “kinky hair disease,” is an inherited disorder of copper metabolism. A baby with this disease can seem normal at birth, except for peculiar hair that is a light tan-orange and kinky and exhibits twisted hair shafts.

The baby soon fails to meet milestones of development, deteriorates neurologically, and dies in childhood.

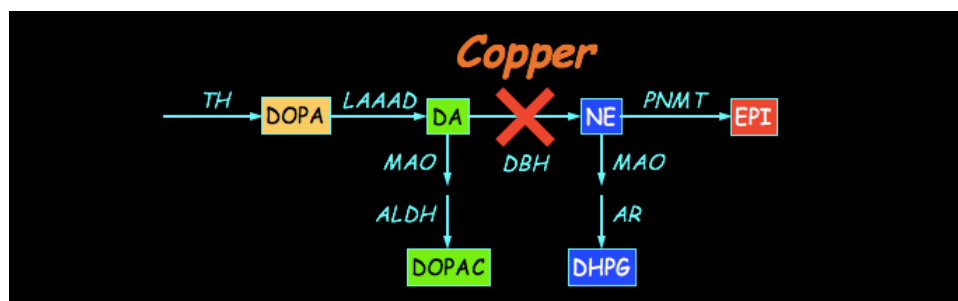
The gene that regulates copper metabolism and is mutated in Menkes disease is located on the X-chromosome.



Menkes disease is also known as “kinky hair disease.”

This means that the disease is confined virtually exclusively to boys.

Copper is required for several important processes in the body. If copper treatment is begun soon enough, Menkes disease patients can have marked improvement in development. In at-risk pregnancies, it is important to diagnose the disease soon after birth, because if the baby had the disease and the disease were caused by a particular mutation, then the baby could respond to injections of copper, but the treatment must begin within a few weeks of birth.



Menkes disease is due to abnormal copper handling in the body. DBH is a copper enzyme.

Detecting this pattern has so far proven perfectly sensitive and

specific in diagnosing the disease in at-risk newborns, enabling successful early copper treatment.



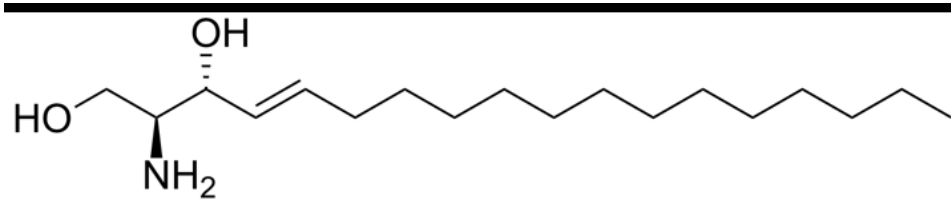
Early copper treatment can markedly improve outcome in Menkes disease.

Copper is necessary for normal activity of the enzyme, dopamine-beta-hydroxylase (DBH), which in turn is required for production of norepinephrine in the body. Patients with Menkes disease all have a characteristic abnormal neurochemical pattern in the plasma, with elevated levels of DOPA, dopamine and its neuronal metabolite DOPAC, compared to levels of norepinephrine and its neuronal metabolite DHPG.

Fabry Disease

Fabry disease is a chronic disease caused by deficiency of the enzyme alpha-galactosidase A. The disease is transmitted as an X-linked trait and affects mainly boys, although girls can be affected.

Alpha-galactosidase A is needed to metabolize lipids, fatty substances that include oils, waxes, and fatty acids. The enzyme deficiency causes accumulation of a type of lipid called sphingolipid. Sphingolipids are fatty acid derivatives of sphingosine.



Chemical structure of sphingosine

Symptoms of Fabry disease usually begin in childhood or adolescence. There are burning sensations in the arms and legs that are exacerbated by exercise and heat exposure.

The lipid storage problem in Fabry disease can produce clouding of the corneas, increased risk of heart attack or stroke, heart enlargement, kidney failure, and gastrointestinal abnormalities.



Angiokeratomas, a characteristic skin finding in Fabry disease

Fabry disease is characterized by angiokeratomas, which are benign tumors of skin capillaries. The tumors appear as small, raised reddish-purple skin blemishes.

Fabry disease is also characterized by anhidrosis (lack of sweating). One can detect anhidrosis in Fabry disease by the quantitative sudomotor axon reflex test (QSART). The abnormal QSART result points to a form of sympathetic cholinergic neuropathy.

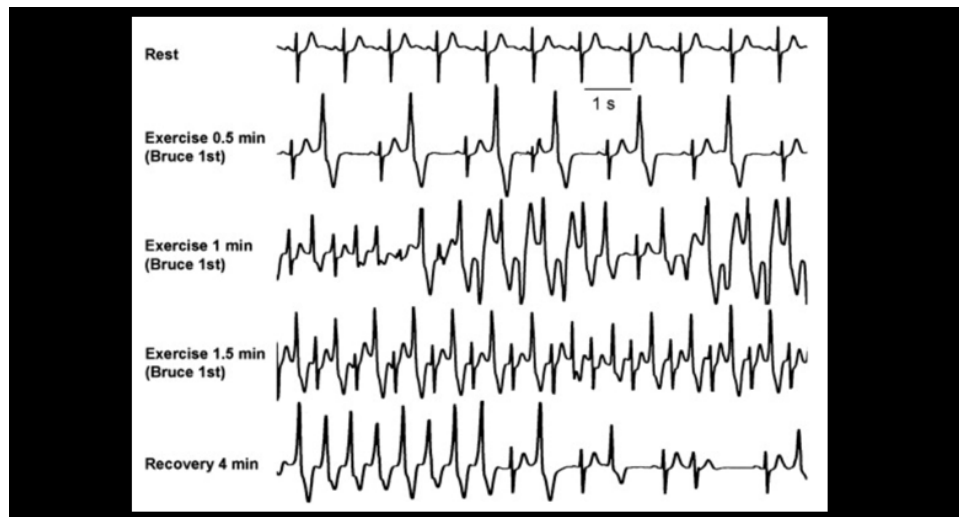
CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a rare genetic disorder in which life-threatening abnormal heart rhythms can be evoked whenever sympathetic noradrenergic system (SNS) or sympathetic adrenergic system (SAS) activity is increased.

Polymorphic ventricular tachycardia can degenerate rapidly to ventricular fibrillation and sudden death. CPVT manifests primarily as emotion- or exercise-related fainting or seizure activity in children and young adults. Importantly, under resting conditions the electrocardiogram is normal.

CPVT is a rare form of inherited fainting that involves a high risk of sudden death from abnormal heart rhythms.

There are two modes of inherited transmission of CPVT, a more common autosomal dominant form and a less common



Exercise-induced ventricular tachycardia in a patient with CPVT.

autosomal recessive form.

In both forms the basis for increased susceptibility to ventricular arrhythmias is enhanced accumulation of ionized calcium in the cytoplasm during SNS activation.

In about a half of CPVT patients a specific causal mutation can be identified. Autosomal dominantly transmitted CPVT is from mutations of the cardiac ryanodine receptor, which is encoded by the *RYR2* gene. Autosomal recessively transmitted CPVT is caused by homozygous mutations (both parents are carriers of the same mutation) or compound heterozygous (the parents have different mutations) in the *CASQ2* gene, which encodes calsequestrin 2.

The main treatment of CPVT is beta-adrenoceptor blockade. Implanted electric cardioverter-defibrillators are also used.

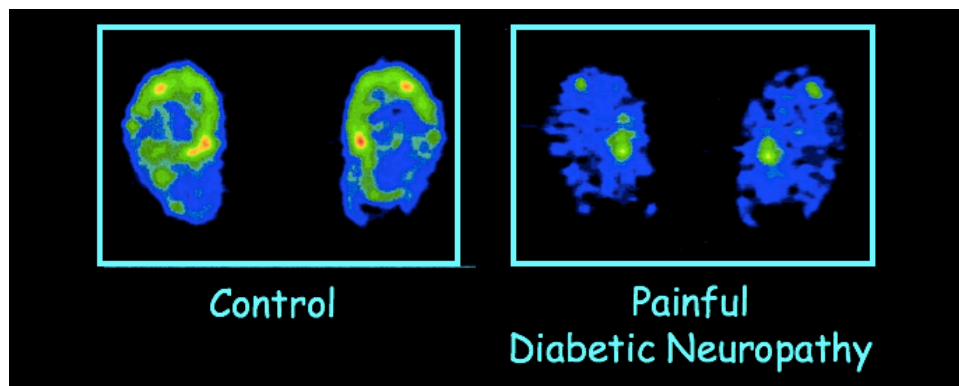
Other proposed treatments include the anti-arrhythmic drug flecainide and left stellate ganglionectomy.

DIABETES

Diabetes is probably the most common cause of autonomic neuropathy. Among patients with diabetes, the occurrence of autonomic neuropathy is an adverse prognostic factor.

Dysautonomia is common in diabetes and is associated with worse outcome.

Diabetic Autonomic Neuropathy



¹⁸F-Dopamine scans at the same level of the feet in a control subject and in a patient with painful diabetic neuropathy. The patient has neuroimaging evidence of loss of sympathetic noradrenergic innervation.

Diabetes often involves chronic pain in the feet (painful diabetic neuropathy). Loss of sympathetic noradrenergic innervation in the feet accompanies the neuropathy.

Diabetics can also have neurogenic orthostatic hypotension, with evidence of failure of baroreflex regulation of sympathetic noradrenergic system outflows.

Poor control of the urinary bladder is another sign of diabetic autonomic neuropathy. Patients have difficulty starting the urinary stream or have urinary retention that can require self-catheterization.

Other manifestations of diabetic autonomic neuropathy include erectile dysfunction, resting tachycardia, diarrhea or constipation, esophageal dysfunction, and decreased stomach contractions (gastroparesis).

Cardiac sympathetic neuroimaging often cannot accurately assess the status of cardiac sympathetic innervation in patients with diabetes, because the disease also involves patchy narrowing of coronary arterioles. Since injected cardiac sympathetic imaging agents are delivered to the heart by way of the coronary arterial tree, it is difficult or impossible to distinguish loss of sympathetic innervation from decreased delivery by the bloodstream.

Mechanisms of diabetic autonomic neuropathy are poorly understood.

The high prevalence, multiple manifestations, and prognostic significance of diabetic autonomic neuropathy contrast with remarkably poor understanding of the mechanisms.

Insulin Neuritis

Another form of neuropathy in diabetes is caused by insulin treatment and has been called insulin neuritis. Insulin neuritis is brought on by a rapid improvement in glucose levels in the setting of long-term high glucose levels (hyperglycemia). In diabetics who have a greater than 4% decrease in their hemoglobin A1c level over 3 months, the risk of developing insulin neuritis exceeds 80%.

The pattern of pain in insulin neuritis follows a “stocking and glove” distribution, with more proximal involvement as the condition worsens. Unlike the usually painful diabetic neuropathy in chronic diabetes, pain in insulin neuritis comes on abruptly. Pathologically, insulin neuritis is a small fiber neuropathy that affects autonomic and sensory non-myelinated fibers. There is also evidence of microvascular disease, as reflected by retinopathy and albumin in the urine.

In addition to pain, patients with insulin neuritis have a high frequency of orthostatic hypotension, lightheadedness, or syncope. In men, erectile failure is also usually present.

Autonomic function testing in insulin neuritis reveals decreased heart rate responses to deep breathing or the Valsalva maneuver and abnormal beat-to-beat blood pressure responses during Phase II and Phase IV of the Valsalva maneuver. These findings fit with baroreflex-cardiovagal and baroreflex-sympathoneural failure.

Hypoglycemia Unawareness

In healthy people, hypoglycemia rapidly activates the sympathetic adrenergic system (SAS), and high circulating epinephrine levels help increase glucose levels. Epinephrine exerts many noticeable effects, such as pallor, sweating, trembling, and a fast pulse rate and augments the experience of distress.

Epinephrine and glucagon are the body's two main glucose counter-regulatory hormones. Patients with type 1 diabetes or severe, insulin-dependent type 2 diabetes have a lack of glucagon release in response to hypoglycemia.

In hypoglycemia unawareness there is a failure of hypoglycemia to trigger epinephrine secretion. Because of this, the patient does not feel the characteristic warning symptoms of low blood glucose levels. There can be prolonged, severe hypoglycemia that results in seizures, syncope, or brain damage.

Hypoglycemia unawareness goes away after 2 to 3 weeks of careful avoidance of hypoglycemia.

The mechanism by which hypoglycemia shifts the threshold for SAS activation to lower plasma glucose concentrations is unknown.

HYPERTENSION

Hypertension, or chronic high blood pressure, increases the risks of serious conditions such as stroke, heart attack, and heart or kidney failure. High blood pressure is defined by abnormal numbers. The systolic pressure is the maximum pressure in the arteries when the heart is ejecting blood. The diastolic pressure is the minimum pressure when the heart is filling with blood between heartbeats.

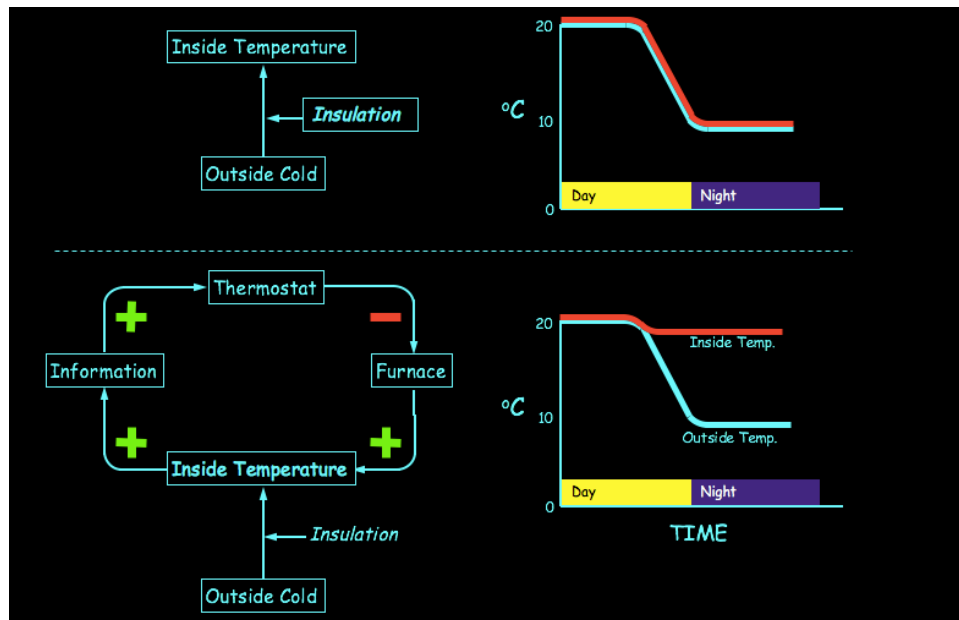
A person with blood pressure persistently more than 140/90 mmHg may be considered to be hypertensive; however, the medical risks, and therefore the need for treatment, depend not only on the blood pressure itself but also on other factors such as age, gender, ethnicity, and co-morbidities such as coronary artery disease, diabetes, or obesity.

In order to understand the role of the autonomic nervous system in hypertension, you have to know about negative feedback regulation.

According to Cannon's concept of homeostasis, the body's many internal variables, such as blood pressure, are not allowed to vary by much or for long. This is because of negative feedback regulation. In a negative feedback loop, there are an odd number of negative relationships in the loop. The level of the monitored variable is maintained.

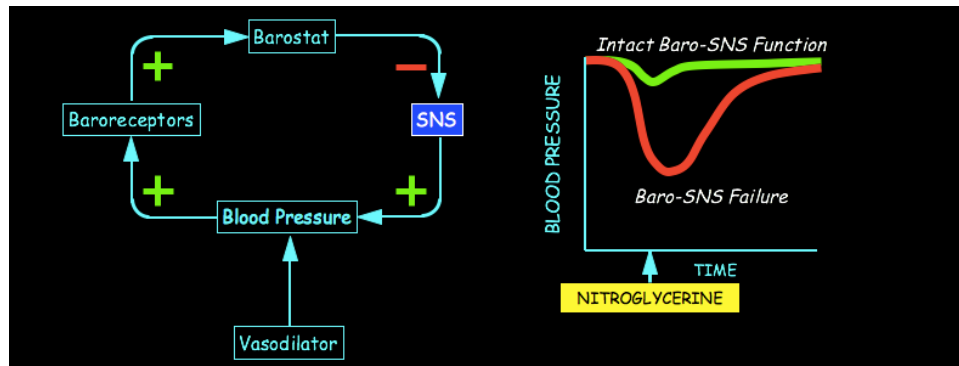
Think of the thermostat in your house. The thermostat compares the information coming in about room temperature

with the setting determined by a controller—namely, you. When the room temperature decreases sufficiently and for long enough, the thermostat senses the discrepancy between what the room temperature is and what the thermostat setting is. The furnace is then instructed to turn on, and the room temperature increases toward the set value.



A thermostatic system is a classic example of negative feedback regulation.

There is a theory that the brain has many comparators that act like thermostats. Taken together, they are called homeostats. According to this theory, a “barostat” in the lower brainstem compares information coming in from baroreceptors about blood pressure with settings determined by higher centers in the brain, and when the discrepancy between what is sensed and what is set is detected, traffic in the sympathetic noradrenergic system (SNS) changes, so that the blood pressure stays within range.

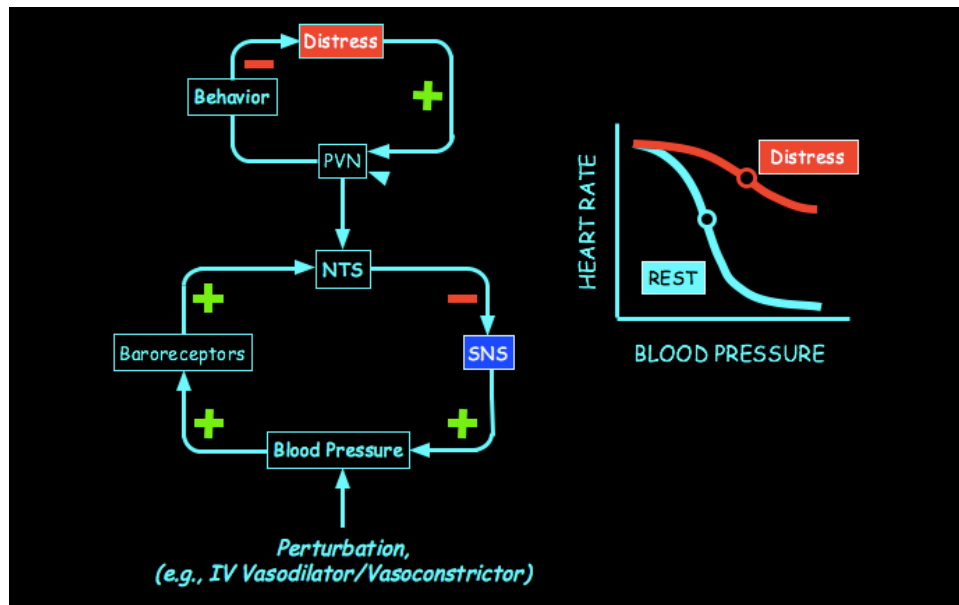


In a patient with baroreflex-sympathoneural failure, IV nitroglycerine produces a large, sustained fall in blood pressure.

For instance, IV injection of nitroglycerine relaxes blood vessels and causes them to dilate (vasodilation), and the blood pressure falls. The barostat receives less baroreceptor afferent information, and the SNS is stimulated reflexively. Because of the increased sympathetic nerve traffic, the rate of release of norepinephrine, the sympathetic neurotransmitter, increases. Then there is more binding of the norepinephrine to alpha-adrenoceptors in the walls of blood vessels, the blood vessels constrict, and the blood pressure rapidly returns to baseline. In the setting of baroreflex-sympathoneural failure, nitroglycerine injection produces a much larger, more sustained decrease in blood pressure.

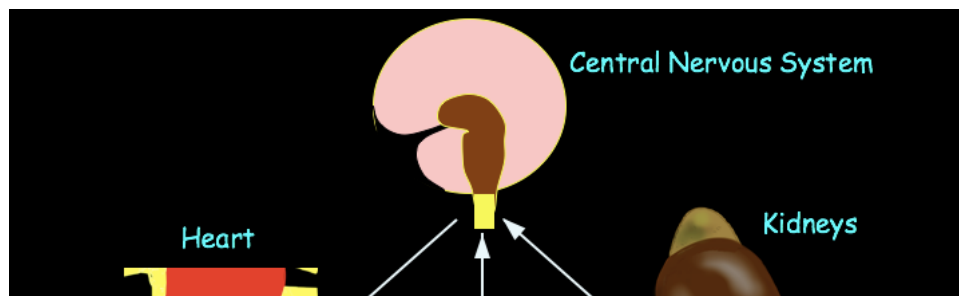
It is important to bear in mind that the barostat, as all homeostats, is conceptual and not real. There are no known physiological comparators, for temperature, blood pressure, glucose, or any other regulated internal variable of the body. Instead, it is likely that there are negative feedback loops at higher centers in the nervous system that affect the functions of those lower down, giving the appearance of altered “instructions” or “set points” for responding.

The nucleus of the solitary tract (NTS) is the site in the lower brainstem that receives all the baroreceptor afferent information. When the NTS neurons receive this information, they direct changes in SNS outflow. In an emotionally threatening situation, activity higher in the brainstem, at the level of the paraventricular nucleus of the hypothalamus (PVN) increases, as part of a kind of neuroendocrine negative feedback loop to enable the organism to deal with the threat. PVN stimulation affects the stimulus-response relationship between blood pressure and the afferent baroreceptor information to the NTS.

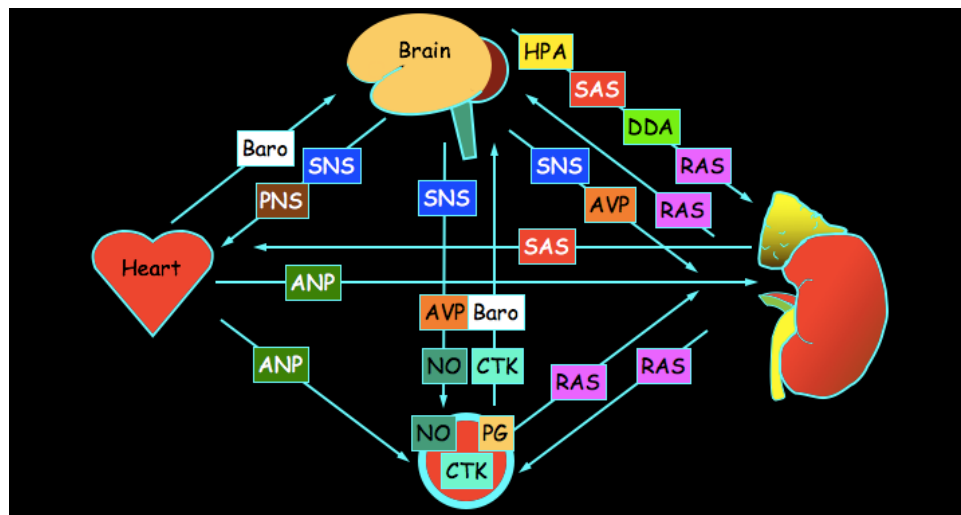


A system that contains a higher level negative feedback loop superimposed on a lower level negative feedback loop can behave as if the lower level loop contained a “homeostat.”

The blood pressure is determined by numerous interactions among the central nervous system, heart, kidneys, adrenal glands, and blood vessels.



The central nervous system, heart, kidneys, and blood vessels interact to determine the blood pressure.



Some effectors participating in regulating blood pressure

The body has many effectors that mediate these interactions.

You probably recognize some of the effectors in the diagram.

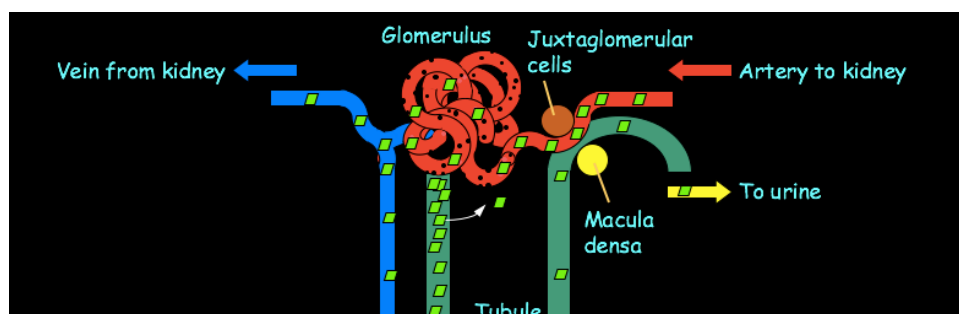
The parasympathetic nervous system (PNS) and the sympathetic noradrenergic system (SNS) use the neurotransmitters acetylcholine and norepinephrine; the sympathetic adrenergic system (SAS) uses the hormone epinephrine, and the renal DOPA/dopamine system (DDA) uses dopamine as an autocrine/paracrine substance. Other effectors include the renin-angiotensin-aldosterone (RAS) system, the hypothalamic-pituitary-adrenocortical (HPA) system, arginine vasopressin (AVP), atrial natriuretic peptide (ANP), nitric oxide (NO), cytokines (CTK), and prostaglandins (PG).

Baroreflex afferents from the heart and large blood vessels (especially the carotid sinus region of the carotid arteries in humans) to the brain provide inhibitory inputs that initiate multiple negative feedback loops.

A complex network involving many chemical messengers acts as if there were a “barostat” that keeps blood pressure within bounds.

Because of the importance of the renin-angiotensin-aldosterone system in blood pressure regulation and in hypertension management, the next section describes this system in more detail.

The renin-angiotensin-aldosterone system (RAS) plays a dominant role in the maintenance of sodium balance in the body. Dietary sodium restriction stimulates RAS activity;



A kidney nephron, emphasizing the juxtaglomerular apparatus

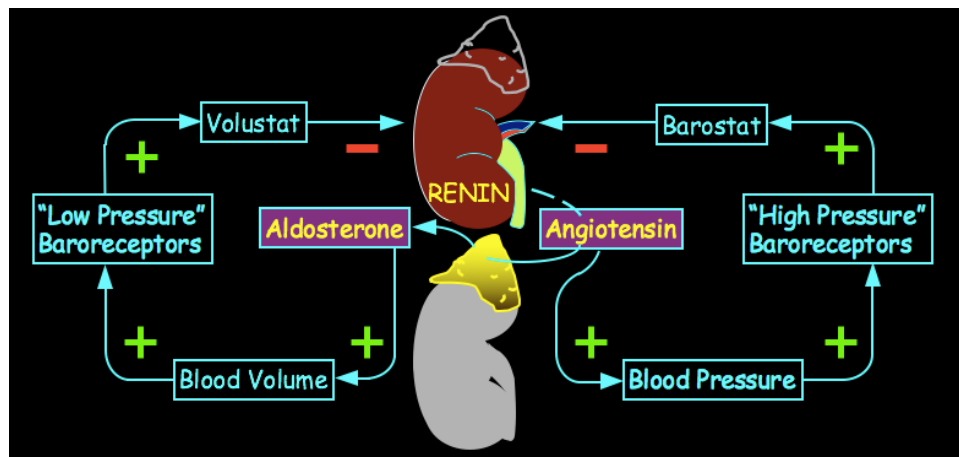
sodium loading virtually shuts it down.

The kidneys filter the blood by millions of leaky blood vessels coiled into tiny ball-like tufts called glomeruli (singular, glomerulus). Blood cells themselves normally cannot pass through the holes in the glomeruli, but the watery part of the blood, containing sodium, does pass through. The filtered fluid (filtrate) then enters tiny tubes, tubules. Cells lining the tubules take up the filtered sodium and return it the bloodstream. The sodium that escapes this recycling stays in the filtrate and eventually leaves the body in the excreted urine.

Specialized tubule cells called the macula densa (from the Latin for “dense spot”) monitor the concentration of sodium in the filtrate that has passed through the glomeruli. When the amount of sodium falls below a certain level, the macula densa cells send a message to other nearby cells, called juxtaglomerular cells, located in the walls of the blood vessels heading toward the glomeruli. The juxtaglomerular cells release into the bloodstream the first effector chemical of the

RAS, renin—the first step of a negative feedback loop.

The same juxtaglomerular cells also act as sensors themselves. They detect stretch, and therefore the distending pressure, in the blood vessels. A fall in the distending pressure leads to release of renin. This means that not just one but at least two homeostats regulate the RAS in the kidneys by negative feedback. The variables that are kept within bounds are the pressure in the blood vessels approaching the glomeruli and the concentration of sodium in the glomerular filtrate.



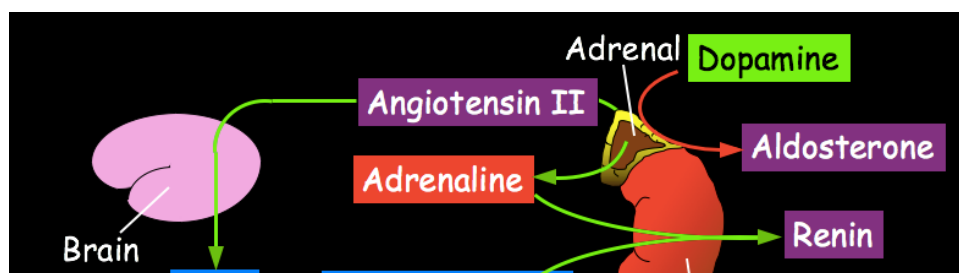
Relationships of components of the renin-angiotensin-aldosterone system to the “volustat” and “barostat”

Stretch receptors in two other places outside the kidneys also contribute to regulation of release of renin. “Low-pressure” baroreceptors are located in the walls of the chambers and veins at the entry to the heart. “High-pressure” baroreceptors are located in major arteries, especially in the carotid sinus, where the common carotid artery splits into the external and internal carotid arteries. When the amount of blood filling the heart falls, such as by a fall in blood volume, or when the blood pressure in the carotid arteries falls, such as from relaxation of

blood vessels, the brain acts on this information to direct an increase in renin release. Conceptually, the homeostat that regulates renin release to maintain blood volume as monitored by the low-pressure baroreceptors can be called the “volustat,” and the homeostat that regulates renin release to maintain blood pressure as monitored by the high-pressure baroreceptors can be called the “barostat.”

Renin has no known activity of its own, but it does act as an enzyme to speed up the conversion of a protein, angiotensinogen, to a peptide (a short chain of amino acids) called angiotensin I. Angiotensin I also has no known physiological action, but another enzyme, angiotensin-converting enzyme (ACE), speeds up the conversion of angiotensin I to angiotensin II. Angiotensin II is one of the most potent chemicals of the body that constrict blood vessels. Angiotensin II therefore increases blood pressure. Predictably, both ACE inhibitors and angiotensin II receptor blockers are effective and widely used to treat hypertension. Another key effect of angiotensin II, which establishes the RAS as the body’s main system regulating sodium balance, is to stimulate the adrenal cortex to release aldosterone. Aldosterone increases reabsorption of sodium from the tubules in the kidneys.

Activation of the RAS therefore increases the blood pressure by constricting blood vessels, via the vasoconstrictor effect of angiotensin II, and also increases the blood volume and cardiac filling, via the sodium retention produced by aldosterone. Thus, the renin-angiotensin-aldosterone system is a key effector for two homeostatic systems, the barostat and the volustat.



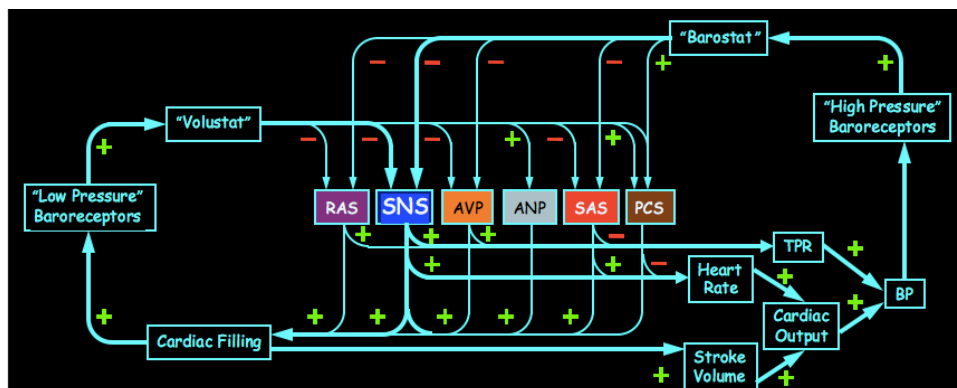
Interactions between catecholamine systems and the renin-angiotensin-aldosterone system

Catecholamine systems of the body interact with the renin-angiotensin-aldosterone system in several ways. First, stimulation of the sympathetic noradrenergic system increases renin secretion. Second, angiotensin II acts in the brain to increase sympathetic nervous outflows. Third, there are abundant angiotensin II receptors in the adrenal medulla. Angiotensin II can evoke release of adrenaline directly, and adrenaline increases renin secretion. Fourth, dopamine, which is the chemical precursor of norepinephrine and adrenaline, inhibits aldosterone secretion from the adrenal cortex in response to angiotensin II.

Blood pressure is determined by two variables. The cardiac output is the amount of blood ejected by the heart in one minute. This corresponds to the total blood flow in the circulation. The total peripheral resistance is the amount of resistance to blood flow in the circulation as a whole.

To get a grasp of cardiac output and total peripheral resistance, think of the pressure in a garden hose. Turning on the faucet increases both the flow of water and the pressure in the hose. If you turned down the faucet, this would decrease the pressure

and the flow. You could bring the pressure back up by tightening the nozzle, but the flow would decrease further. If the nozzle remained tightened, turning the faucet up would increase the flow, but now the pressure in the hose would be high. In most people with chronic hypertension, the cardiac output is normal or even decreased. This means that in hypertension, the high blood pressure is usually from high total peripheral resistance. The vascular nozzle is too tight.



Concept diagram showing negative feedback regulation of blood volume and blood pressure by several effectors

Just as two variables determine blood pressure, two variables determine cardiac output. These are the heart rate and the stroke volume. The heart rate is the number of beats per minute. The stroke volume is the amount of blood ejected by the heart in one heartbeat. The sympathetic noradrenergic system and the renin-angiotensin-aldosterone system are two of the most important effectors in blood pressure regulation. The vagus nerve, the tenth cranial nerve, contributes to blood pressure regulation especially by modulation of heart rate. The sympathetic adrenergic system plays a major role in the high blood pressure commonly found in emergency situations. In addition to the barostat, a volustat regulates blood volume and

thereby cardiac filling and cardiac output, based on information from low pressure baroreceptors. Although the diagram of negative feedback regulation of blood pressure seems very complex, what is depicted actually is a relatively simple model compared to models hypertension researchers have developed.

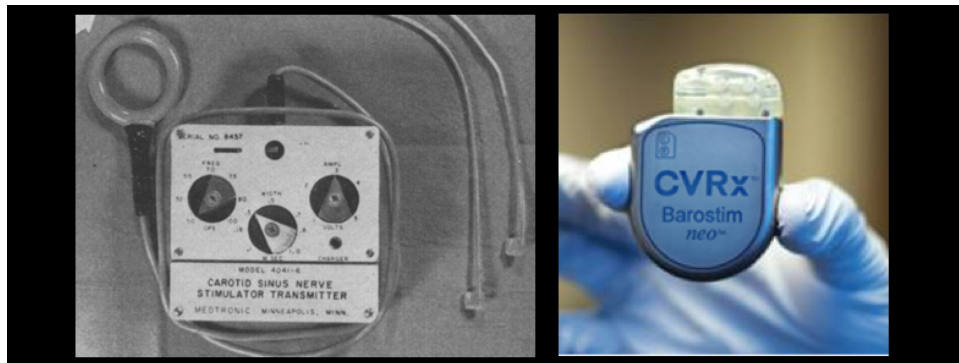
One may ask, if the body has available so many negative feedback loops and effectors to control blood pressure, why does hypertension even exist? What goes wrong with the negative feedback regulation, such that the blood pressure becomes persistently high? Somehow the complex interplay of the blood vessels, heart, kidneys, and the central nervous system goes awry. No one knows exactly what goes wrong, how, or why.

A guess—and it's only a guess—is that the effectors that regulate blood pressure evolved to maintain homeostasis of other internal variables and not blood pressure *per se*. Throughout human evolution, systems evolved to counter infection, to endure emergencies, to maintain the core temperature of the body, to distribute blood flows to body organs appropriately in different circumstances, to convert ingested food to energy and get rid of waste, to have correct levels of several electrolytes such as sodium, and to conserve water. These all have offered clear survival advantages. The side effect of increased blood pressure may have had relatively little significance. In modern society, these needs no longer are pressing, but the homeostatic systems may still operate in a manner that biases toward high intake of fat, sugar, salt, and water, with attendant increased blood pressure. Hypertension might then be a consequence of modern civilization.

Carotid Sinus Stimulation

Until relatively recently it was thought that despite the importance of the arterial baroreflex for keeping the blood pressure within a pre-specified range acutely, the arterial baroreflex does not contribute to the long-term regulation of blood pressure, because of “resetting” of the reflex as a consequence of hypertension.

Findings from recent studies about carotid sinus stimulation have forced reconsideration of this dismissal of the arterial baroreflex as a determinant of long-term blood pressure regulation.



Modern day carotid sinus stimulation is a descendant of the “Baropacer,” which was an external pacemaker developed in the 1960s. The electrodes of the Baropacer were wrapped around the Modern implanted carotid sinus stimulators are descendants of “baropacer” devices of the 1960s.

Early in my career in Building 10, the NIH Clinical Center, the Cardiology Branch of the National Heart, Lung, and Blood Institute was located on the 7th floor. I was allowed to use a “Baropacer” from the Branch’s animal lab for an experiment

designed to map out brain pathways mediating the baroreflex by stimulating the carotid sinus nerve of cats. The experiment was a failure, mainly because of the inability to maintain the integrity of the nerve over time. Modern implanted baropacers such as the CVRx neo™ are placed on the carotid sinuses—a much simpler approach than wrapping the electrodes around the nerves—but this seems to be an effective approach.

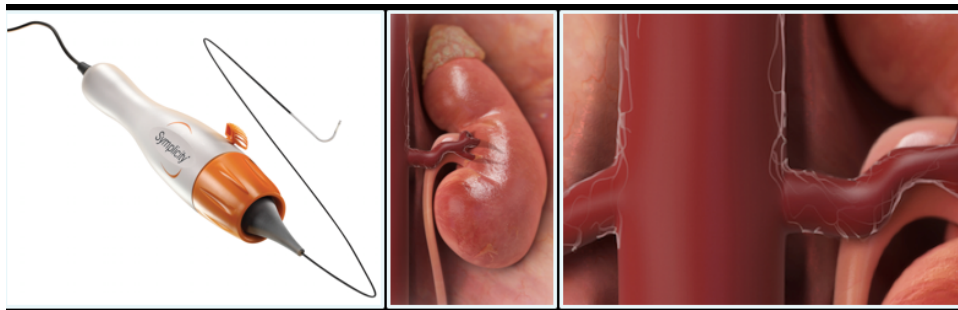
Carotid sinus stimulation is currently undergoing clinical trials to treat refractory hypertension. The stimulation is continuous. It has several other potential uses (that was funny), including treatment for heart failure, some arrhythmias, and metabolic syndrome, all based on inhibition of sympathetic noradrenergic outflows by stimulating baroreflex afferent traffic.

Similar technology might be developed to treat supine hypertension in patients with neurogenic orthostatic hypotension from chronic autonomic failure—a very difficult condition for which no drug is effective.

Renal Nerve Ablation

Another technology undergoing testing to treat refractory hypertension is based on destroying the sympathetic nerves supplying the kidneys. The procedure involves percutaneous cannulation of the renal arteries and delivery of radiofrequency energy in a spiral through the walls of the arteries. This destroys the nerves that travel in the outer layer of the arterial walls.

Medtronic, the company that manufactured the Baropacer in the



Medtronic's Symplicity system for renal sympathetic nerve ablation.

1960s, sponsored a recent large trial of its Symplicity™ device for renal nerve ablation. The trial was stopped because of lack of efficacy. Further development of this technology may require devising means to test the extent of renal denervation actually produced by the procedure.

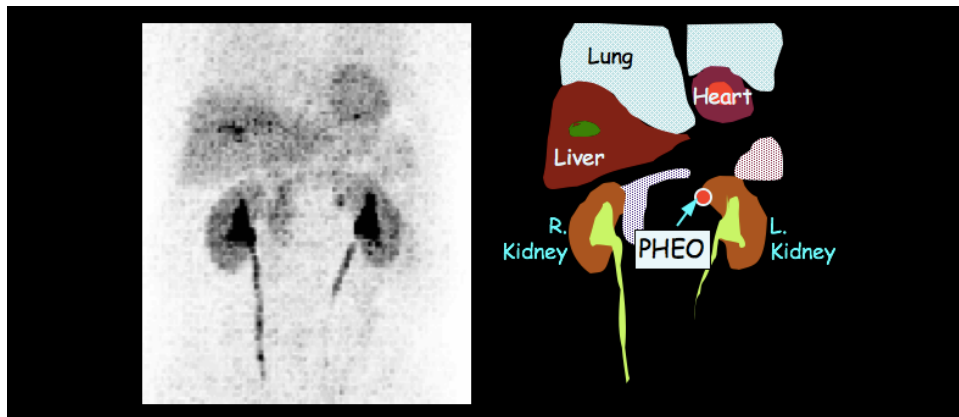
Hypertension has many mechanisms. It is possible that only patients with a substantial sympathoneural contribution to their high blood pressure (hypernoradrenergic hypertension) would benefit from renal nerve ablation. Such patients could be identified by clonidine suppression testing.

Pheochromocytoma (Pheo)

Pheochromocytomas (“pheos”) are rare but clinically and scientifically important tumors of cells that produce and secrete catecholamines.

“Pheos” are rare tumors of cells that make catecholamines.

Most pheos are located in the adrenal gland. Because of the potent effects of catecholamines on the cardiovascular system, pheos often present with signs and symptoms of high circulating catecholamine levels. These include high blood pressure, headache, pallor, and sweating.



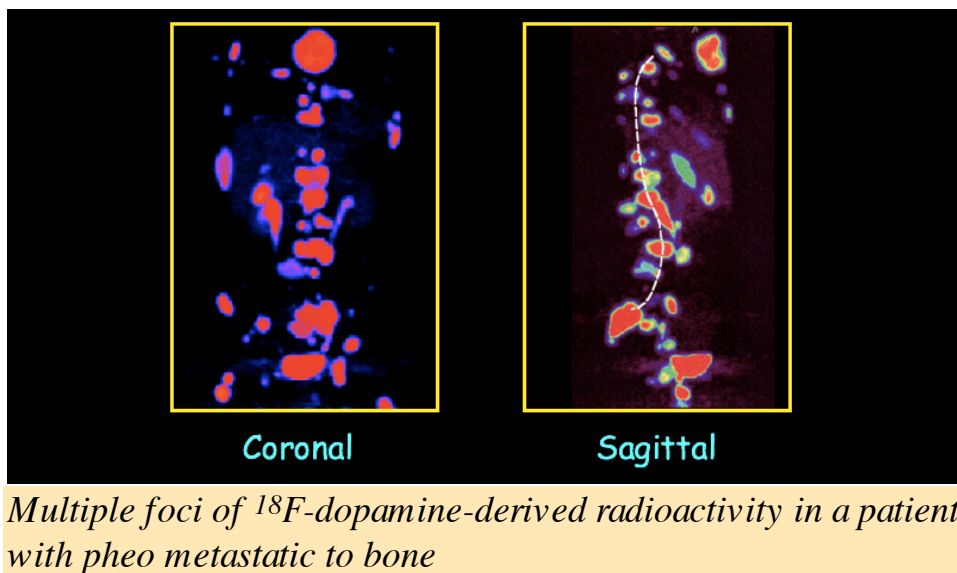
Pheochromocytomas (“pheos”) usually are in an adrenal gland.

A patient harboring a pheo can have unexpected, paroxysmal hypertension upon exposure to relatively mild perturbations, such as anesthesia induction, or administration of drugs such as sympathomimetic amines.

Most pheos are benign and can be removed surgically. This means that pheos represent a potentially curable form of hypertension.

In a patient with clinical findings suggestive of a pheo, measuring plasma levels of free (unconjugated) metanephrines (normetanephrine and metanephrine) is a valuable screening test, because of the extremely low frequency of false-negative results. That is, if plasma metanephrines are normal, one can rule out pheo.

If the screening biochemical testing is positive, then MRI, CT scanning, clonidine suppression testing, or imaging with a ligand for the cell membrane norepinephrine transporter (e.g., ^{123}I -MIBG) may be done.



Clonidine decreases sympathetic noradrenergic outflows and thereby decreases plasma norepinephrine (NE) levels. If a patient had high blood pressure due to high sympathetic noradrenergic system outflows, then clonidine would produce a large decrease in the plasma NE. In a positive clonidine suppression test for a pheo, the plasma NE level fails to decrease between baseline and 3 hours after 0.3 mg of oral clonidine.

Rarely, pheochromocytoma is malignant and metastasizes. Metastatic pheo can be detected by a variety of specialized imaging agents and also biochemically by measuring plasma levels of 3-methoxytyramine, the O-methylated metabolite of

dopamine.

STRESS CARDIOPATHY IN A SENATOR

Pheochromocytomas exert sudden, serious adverse effects on the cardiovascular system, due to massive increases in circulating levels of catecholamines in response to seemingly minor manipulations.

I know of the case of a U.S. Senator who went in for routine thyroid surgery but had severe hypertension upon anesthesia induction, and so the surgery was called off. Subsequently he again had a hypertensive episode evoked by anesthesia induction. He went into acute heart failure and had to be treated in an intensive care unit. In an attempt to increase the pumping efficiency of his heart, IV adrenaline was infused. Unexpectedly, this worsened his heart failure, and he almost died. The infusion was stopped, and gradually the patient recovered.

He then underwent a workup for pheo. The workup included ¹⁸F-dopamine PET scanning and measurement of plasma metanephrines at the NIH Clinical Center. Both tests were positive. A pheo was identified surgically and removed safely. Subsequently he had the thyroid surgery he had originally planned on, without complications.

This case teaches a few lessons. First, sudden, unexpected hypertension should raise a suspicion of pheo. Second, increases in plasma levels of catecholamines by a pheo can be sufficiently massive to cause a form of heart failure from stress

cardiopathy (described later). Third, instead of stimulating the heart, adrenaline can precipitate or worsen heart failure due to toxic effects on the myocardial cells. Whether these effects reflect occupation of adrenoceptors on the surface of the cells or entry of adrenaline into the cells and intracellular toxicity remains unclear.

HEART FAILURE

Most dysautonomias are secondary; that is, an alteration in autonomic nervous system function that normally would itself be appropriate, adaptive, and helpful can be rendered maladaptive, harmful, or even lethal in the setting of an independent pathological state.

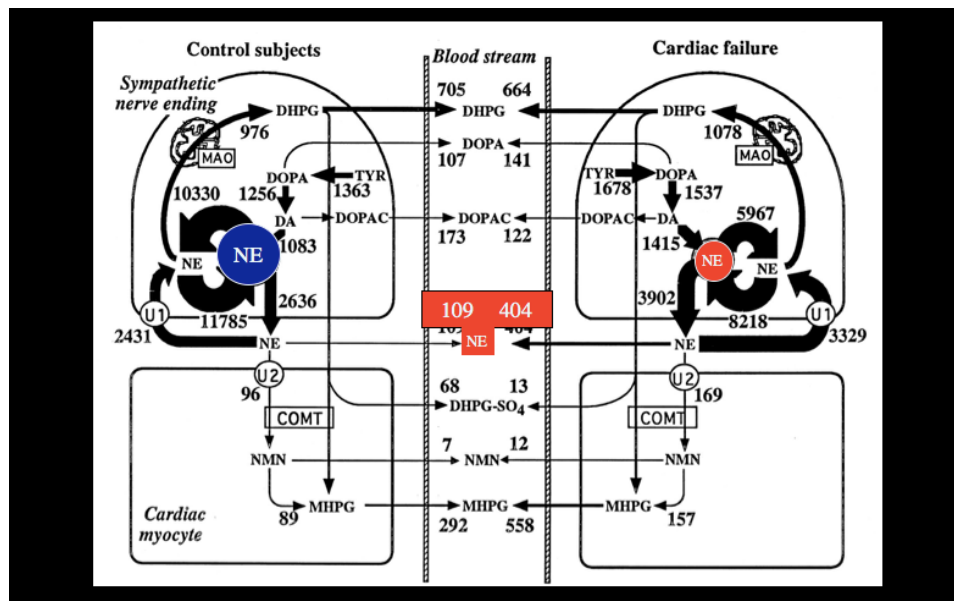
Heart failure is associated with stimulation of the sympathetic noradrenergic system (SNS).

The situation in heart failure provides a good example. In heart failure the heart does not deliver an appropriate amount of blood to body organs. As part of compensation to improve cardiac pump function, the sympathetic noradrenergic system (SNS) is activated. At the same time that this can improve the pump function of the heart, however, SNS activation increases the risk of abnormal heart rhythms, increases the work of the heart, promotes retention of sodium by the kidneys, and promotes overgrowth of heart muscle, which can stiffen the heart walls and worsen the heart failure.

The pattern of pathophysiologic abnormalities of the SNS in

heart failure is very complex. At the same time that there is increased release of norepinephrine (NE) in the failing heart, there is also depletion of NE stores.

Energy-requiring processes such as Uptake-1 and vesicular uptake are less efficient in heart failure. Decreased NE stores in the failing heart appear to result from high NE turnover and



Heart failure involves increased norepinephrine release from sympathetic nerves at the same time that there is depletion of norepinephrine stores. Several other abnormalities are found.

reduced efficiency of NE reuptake and storage. Meanwhile, it is thought that the high rate of delivery of NE to its receptors renders the beta-1 adrenoceptors less sensitive.

Thinking in terms of “cybernetic medicine” (in the past I’ve called it “scientific integrative medicine”) can help grasp the development and progression of chronic heart failure. Suppose

a person was born with a bicuspid aortic valve—the most common congenital valvular lesion in humans. The abnormal anatomy would cause turbulent blood flow across the valve. This might produce a “functional” heart murmur, but the individual could develop normally. Over the years of turbulent blood flow with each heartbeat, wear and tear on the valve would cause it to calcify and become stenotic, decreasing aortic filling. Via a negative feedback loop involving release of the sympathetic noradrenergic system (SNS) from baroreceptor restraint, the brain would direct a compensatory increase in cardiac SNS outflow. Increased norepinephrine (NE) delivery to its receptors on myocardial cells could help maintain cardiac function for many years.

In the long run, however, these compensatory, adaptive responses could come at a cost. NE promotes myocardial hypertrophy, which increases the demand for oxygen and metabolic fuels delivered by coronary perfusion; it increases cardiac contractility, which in this case would maintain aortic filling at the expense of increased blood flow turbulence and wear and tear on the valve, accelerating the stenosis; and it reduces thresholds for abnormal heart rhythms (arrhythmias).

Especially in the setting of concurrent coronary artery disease, the increased demand for oxygen by the stimulated, hypertrophied heart could at times of stress exceed the supply—a kind of energy crisis, manifested clinically by easy fatigue and dyspnea on exertion among other symptoms. In sympathetic nerves, NE stored in vesicles leaks spontaneously continuously into the cytosol, and reuptake of NE back into the vesicles requires energy. As a consequence of decreased energy availability there would be decreased NE recycling and

depletion of NE stores. This would limit NE release during stress and escalate further the increases in SNS outflows. Inefficient sequestration of catecholamines that leak passively from the vesicles into the cytosol could result also in buildup of catecholamines in the cytosol, where they can be rendered “autotoxic” by spontaneous and enzymatic oxidation to form toxic byproducts. Destruction of sympathetic nerves due to autotoxicity would diminish further the stores of releasable NE. Reuptake of released NE back into the terminals would be attenuated concurrently, because neuronal reuptake is also an energy-requiring process. The patient would now have congestive heart failure.

Once cardiac pump function declined to below a certain level despite maximal SNS stimulation, blood would back up into the pulmonary veins, bringing on pulmonary edema. The patient would then become short of breath even at rest and, in a distress response, experience the classic “feeling of impending doom,” which has been associated from time immemorial with massive activation of the sympathetic adrenergic system (SAS) and adrenomedullary release of adrenaline. Moreover, rather than augmenting left ventricular myocardial contractility, too much adrenaline is toxic to myocardial cells. Myocardial contractility would decrease further, “stress cardiopathy” would set in, and the pulmonary edema would worsen. In several ways, physiologic negative feedback loops would have now given way to pathophysiologic positive feedback loops. Within a sometimes surprisingly short period of time from the onset of symptoms, the patient could die—within minutes because of a catecholamine-evoked ventricular arrhythmia, hours because of intractable pulmonary edema, or days because of critically decreased perfusion of body organs such as the kidneys.

STRESS CARDIOPATHY

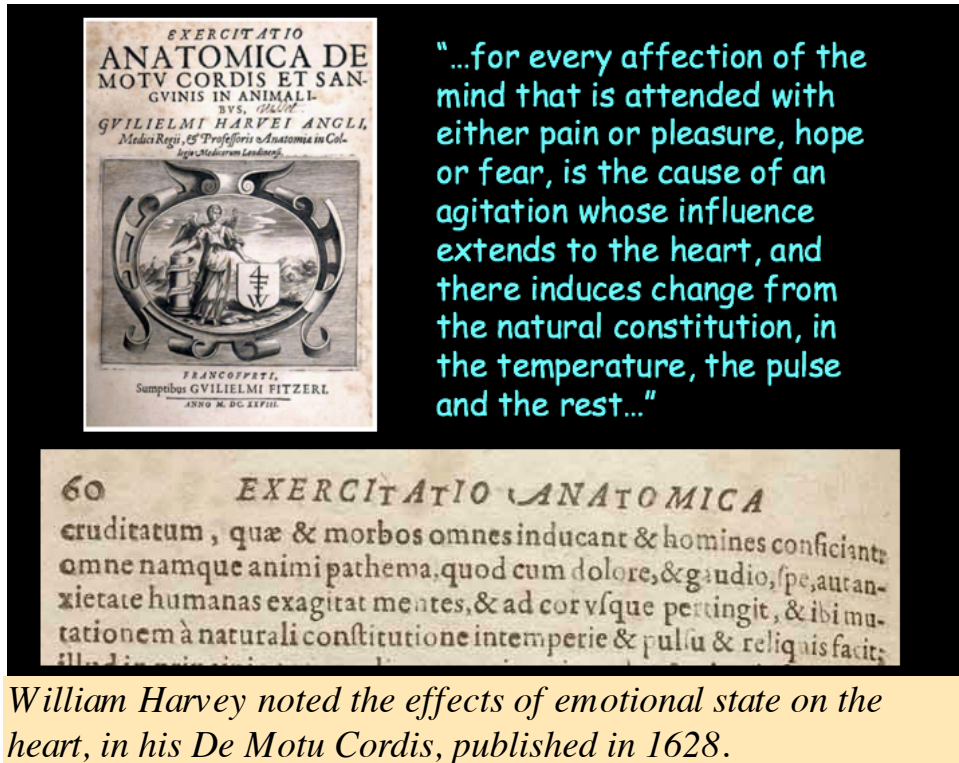
All emotions entail changes in heart functions, a fact recognized by one of the giants in the history of medicine and physiology, William Harvey.



William Harvey, father of clinical physiology and neurocardiology

In 1628 in his book, *On the Circulation of the Blood*, a classic in the history of clinical science, Harvey described the circulation of the blood for the first time.

Remarkably, in the same book Harvey stated one of the founding ideas of psychosomatic medicine, neurocardiology, and autonomic medicine: "...for every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart..."



Pathological studies about how distress can produce sudden death were not done until the past century. In 1907, about twelve years after the discovery of the cardiovascular stimulatory effects of adrenaline, it was demonstrated that infusion of adrenaline can lead to death of heart muscle. The heart muscle cells rupture and die of overstraining. A particular microscopic change called "contraction band necrosis" develops. In victims of assault who die without sufficient evidence of internal or external injury to explain the death, most have contraction band necrosis as part of the post-mortem findings. Similarly, patients who die from a stroke due to bleeding inside the brain often have contraction band necrosis (also called myocytolysis) of heart muscle cells. The extent of

loss of heart muscle cells in this setting is related to the extent

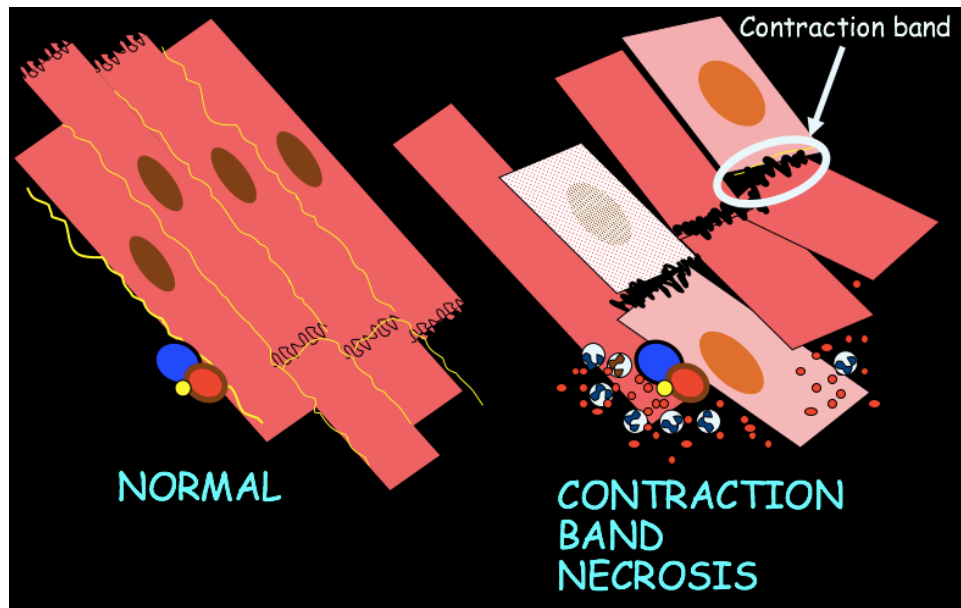


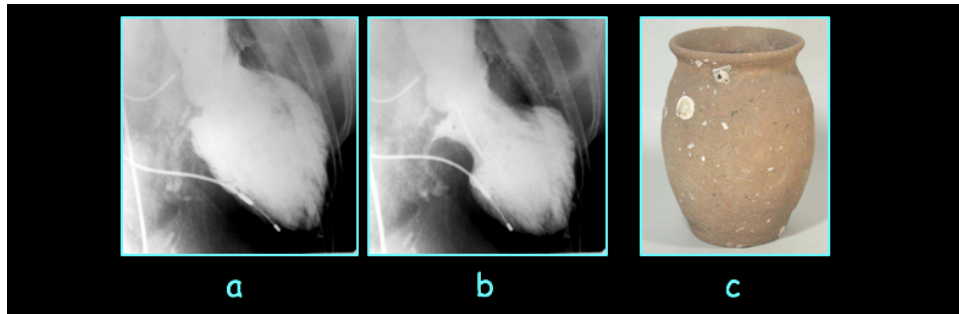
Diagram of contraction band necrosis of heart muscle cells

of increase in plasma levels of catecholamines.

***Takotsubo* Cardiopathy**

A relatively recently described form of distress-induced acute heart failure is *takotsubo* cardiopathy, so named because of a characteristic abnormal shape of the heart in patients with this condition.

A *takotsubo* is a Japanese pottery urn used to catch octopuses. The octopus's head gets stuck in the jar (I guess, at least in this respect, octopuses are not that smart.) In *takotsubo* cardiopathy, during systole when the heart is ejecting blood, the apex of the heart balloons out while the base of the heart contracts normally. On a ventriculogram the combination of



In takotsubo cardiopathy, during systole the apex of the heart balloons out.

apical ballooning and basal contraction gives the appearance of a *takotsubo*.

Takotsubo cardiopathy has been reported to occur mainly in post-menopausal women, for reasons that are not yet completely understood. Some patients can have acute catecholamine-induced heart failure without the *takotsubo* heart shape.

Remarkably, if the patient survives, heart muscle function can recover over a couple of weeks.

Patients with stress cardiopathy have extremely high plasma adrenaline levels—more than 30 times normal. It seems likely that adrenaline levels this high are directly toxic to the heart.

In the setting of circulatory shock related to poor heart muscle pumping, catecholamines such as adrenaline often are given IV to try to improve the contractile function of the heart. Sometimes this approach backfires, and the infusion actually worsens the heart's pumping capability. This situation is very

tenuous because of the possibility of induction of a lethal positive feedback loop.

Although it is widely accepted that high circulating adrenaline levels can cause or contribute to stress cardiopathy, the mechanisms of adrenaline cardiotoxicity are poorly understood. There are a few possibilities. First, at high concentrations adrenaline may inhibit rather than stimulate production of the second messenger adenylyl cyclase, by a switch from a stimulatory to an inhibitory G-protein. Second, adrenaline taken up into the heart muscle cells could undergo spontaneous or enzyme-catalyzed oxidation, resulting in formation of autotoxic metabolites that interfere with the functions of numerous proteins required for cellular integrity. Third, adrenaline-mediated, drastically increased entry of ionized calcium into the cytoplasm could so contract the cells that they rupture—hence the term, “contraction band necrosis.”

CHRONIC ORTHOSTATIC INTOLERANCE

Autonomically Mediated Syncope

Synopsis:

Mainly young adult women or children.

Normal pulse rate during standing.

Can be associated with several non-specific associated problems (inability to tolerate prolonged standing, heat intolerance, fatigue, chest pain, heart “flip-flops,” exercise intolerance).

Variable outlook, can improve.

Not life-threatening.

Syncope is sudden loss of consciousness (you black out) that is associated with loss of muscle tone (you go limp) and reverses rapidly (you wake up quickly.)

Syncope is sudden loss of consciousness associated with loss of muscle tone and the regaining of consciousness within seconds to minutes. In pre-syncope, the patient feels like he or she will faint but does not actually lose consciousness.

Fainting is by far the most common cause of sudden loss of consciousness in the general population. It occurs predominantly in young adults and is more common in women than in men. In elderly adults, syncope is more likely to be a

sign of a heart problem (abnormal heart rhythm, abnormal conduction of electrical impulses in the heart, or heart valve problem) or orthostatic hypotension.

In people with intact adrenal glands, autonomically mediated syncope is characterized by an increase in plasma adrenaline levels.

I use the term, autonomically mediated syncope because of the key role of alterations in activities of the components of the autonomic nervous system in fainting.

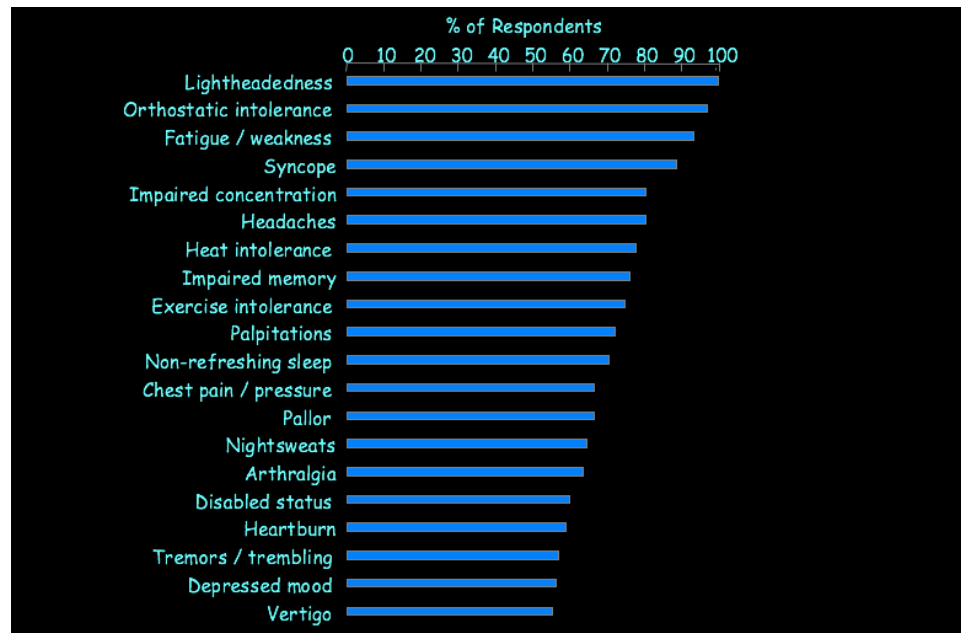
Many patients with frequent episodes of autonomically mediated syncope recognize early symptoms and signs of a fainting reaction coming on and are able to abort the episode before frank loss of consciousness actually occurs.

Autonomically mediated syncope is fainting. Other names are vasovagal syncope, vasodepressor syncope, neurally mediated hypotension, reflex syncope, and neurocardiogenic syncope. Pre-syncope is near-fainting but without actual loss of consciousness.

Patients in whom autonomically mediated syncope is a frequent problem often feel unwell between episodes, with an inability to tolerate prolonged standing, chronic fatigue, headache, “brain fog,” or chest pain.

Frequent autonomically mediated syncope can resemble POTS. Both conditions mainly involve young adult women, and both

are associated with inability to tolerate prolonged standing, chronic fatigue, headache, and chest pain. POTS more commonly involves symptoms of dysfunction in multiple body systems.



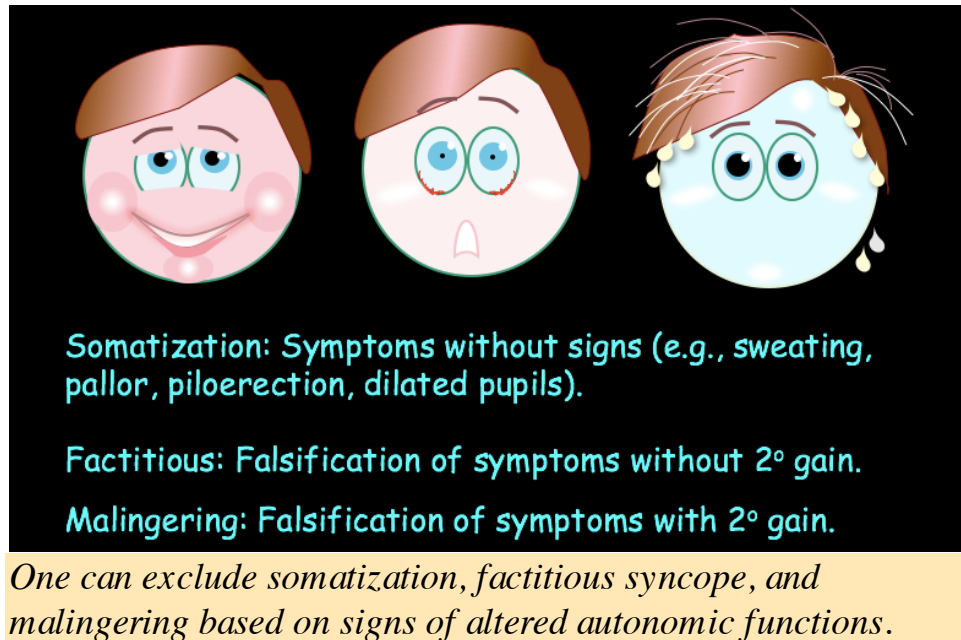
Patients with frequent episodes of autonomically mediated syncope usually have many other symptoms.

Tilt table testing can provoke a sudden fall in blood pressure, called neurally mediated hypotension (NMH), in patients with POTS or autonomically mediated syncope.

As in POTS, in autonomically mediated syncope there does not seem to be much risk of the later development of a chronic cardiovascular or neurodegenerative disease.

Clinicians often wonder about somatization, factitious fainting, or malingering in patients with frequent episodes of fainting. Seeing signs of adrenaline excess such as pallor, sweating,

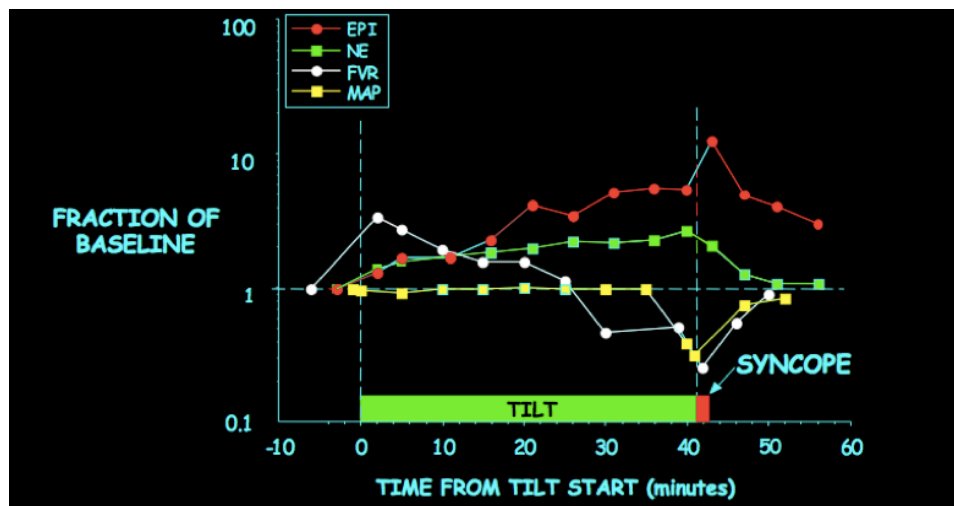
piloerection, and pupillary dilation can help settle the matter.



SYMPATHOADRENAL IMBALANCE

Regardless of the underlying diagnosis, autonomically mediated syncope seems to have the same proximate mechanism. There is a larger increase in sympathetic adrenergic system (SAS) outflow than in sympathetic noradrenergic system (SNS) outflow— “sympathoadrenal imbalance,” or SAI.

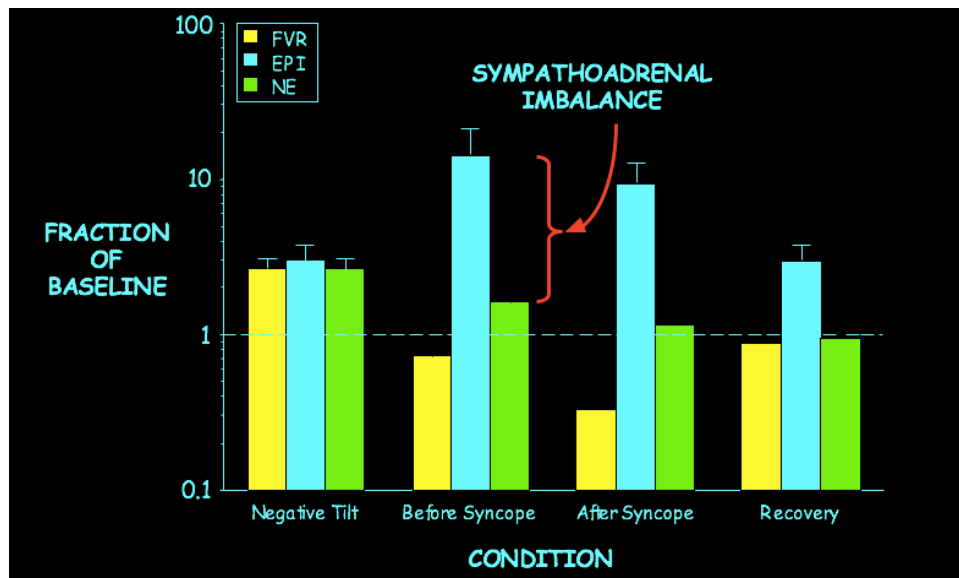
The neurochemical hallmark of SAI is a proportionately greater increase in the plasma adrenaline level than in the simultaneously measured plasma norepinephrine level. SAI typically not only accompanies but precedes episodes of autonomically mediated syncope, suggesting that SAI is a causal factor in fainting.



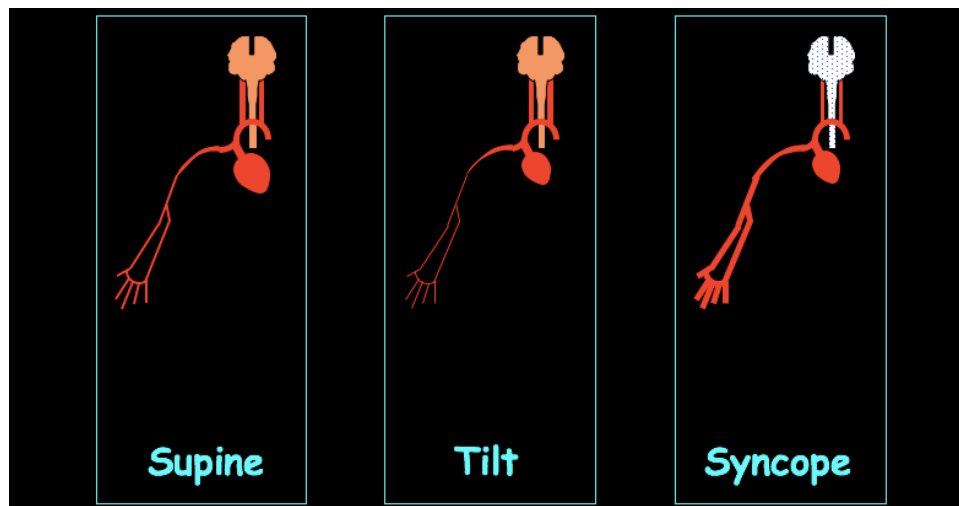
Tilt-induced neurally mediated hypotension and syncope. Note the decrease in forearm vascular resistance (FVR) and mirror image increase in plasma epinephrine (EPI) and greater increase in EPI than norepinephrine (NE)—i.e., “sympathoadrenal imbalance”—before the fall in mean arterial pressure (MAP).

Injection of adrenaline into a healthy person does not evoke fainting. This is because skeletal muscle vasodilation produced by adrenaline’s action at beta-2 adrenoceptors on the vascular smooth muscle cells is normally countered by reflexive stimulation of sympathetic noradrenergic system (SNS) outflows. Norepinephrine (NE) is then released at an increased rate from SNS nerves supplying the skeletal muscle, and the released NE occupies alpha-1 adrenoceptors on the vascular smooth muscle cells, resulting in a counter-balancing vasoconstrictor effect. In autonomically mediated syncope, SNS outflow does not keep up with the adrenaline-induced skeletal muscle vasodilation.

It has been proposed that in SAI, adrenaline-induced skeletal



Autonomically mediated syncope involves a pattern where before the acute episode, epinephrine (adrenaline) levels are high, while the sympathetic noradrenergic system is less activated or even shuts down.



Concept diagram illustrating changes in blood flow distribution accompanying tilt-induced autonomically mediated syncope

muscle vasodilation is not countered by increased SNS outflow.

The cardiac output is redistributed toward the skeletal muscle, at the expense of delivery of blood to the brain.

Increased sweating also precedes autonomically mediated syncope. Although this can occur at the same time as SAI, it has not yet been shown that adrenaline evokes the sweating. Pallor constitutes another classic sign in autonomically mediated syncope. Pallor in this setting may be due to the cutaneous vasoconstriction evoked by high circulating adrenaline levels. High circulating adrenaline levels could also explain the dilated pupils typically noted when people faint.

DO SNAKES FAINT?

The ability to stand up enabled the evolution of some of the defining characteristics of us humans. Adopting an upright posture, however, has also posed a challenge—maintaining blood flow to the brain despite gravitational pooling of blood in the legs and pelvic organs. To redistribute blood rapidly and appropriately in this setting, hormonal systems do not suffice; a nerve network is required.

In evolutionary terms, our ancestors began standing upright relatively recently. This may help explain why only one such nerve network seems to have evolved in humans—the sympathetic noradrenergic system (SNS).

Each time you stand up, the SNS is activated markedly, rapidly, unconsciously, and automatically. By release of the chemical messenger, norepinephrine (NE), from nerve terminals in the walls of blood vessels in the limbs, kidneys, and gut, blood

vessels in these organs constrict, while blood vessels in the heart, lungs, and brain do not. Blood flows to the brain, heart, and lungs therefore are preserved during standing up, despite the fall in venous return to the heart.



Harvey B. Lillywhite and examples of climbing and water snakes

In forms of dysautonomia where the SNS fails, norepinephrine release does not increase adequately when the patient stands up. Possibly because of the novelty of the challenge in evolution, there are no alternative effectors for immediate compensatory activation. The tone of blood vessels in the skeletal muscle, kidneys, and gut does not increase, and as the venous return to the heart falls, so does the blood pressure. This explains why orthostatic hypotension constitutes a cardinal manifestation of failure of the SNS.

Climbing snakes often wriggle up trees, while water snakes spend their lives horizontal, surrounded by about the same pressure from head to tail. Many years ago, Dr. Harvey B. Lillywhite, of the University of Florida at Gainesville, placed snakes into cylindrical plastic tubes and then tilted them head-up. Among climbing snakes, nothing much happened, but among water snakes, during the tilting blood pooled in the tail end, the blood pressure at the midpoint of the body fell, and the

heart rate increased compensatorily but inadequately to maintain the blood pressure at the level of the head. If kept in this situation, with a brain blood flow of zero, water snakes would have to lose consciousness eventually.

Structural and functional differences between climbing and water snakes help explain their different abilities to maintain blood flow to the brain during head-up tilting. Climbing snakes have thin, tapered bodies, with the heart located relatively close to the brain. Water snakes have wider and more cylindrical bodies, with the heart close to the longitudinal center. Climbing snakes have higher blood pressure than water snakes, even when horizontal. Climbing snakes also writhe when tilted, squeezing blood in the veins toward the heart like squeezing toothpaste up a tube.

Analogously, in humans who are about to faint while standing up, voluntary muscle pumping, by curling the toes, twisting the legs, and tightening the buttocks, can deliver enough blood to the heart and brain to prevent loss of consciousness temporarily. A patient with frequent fainting I evaluated many years ago obtained virtual cure of the problem by a regimen of isometric calf muscle training.

Climbing snakes when tilted constrict blood vessels to organs and muscles in the lower half of the body but not to vital anterior organs such as the lung, brain, and heart. The blood vessels tailward of the heart in climbing snakes have a substantial nerve supply—presumably sympathetic noradrenergic nerves, but I'm not sure—consistent with the ability to constrict local blood vessels reflexively. In climbing snakes, as in humans, the sympathetic noradrenergic system

seems to have afforded a survival advantage by helping counter effects of gravity on delivery of blood to vital organs and enabling occupation of a particular environmental niche. Considering that water snakes evolved from terrestrial snakes, in evolutionary history the ability to adapt to gravitational stress must have evolved in the species that took to the water.

Some patients who have chronic orthostatic intolerance appear to have a structural problem that predisposes them to fainting while upright. These patients can have evidence for increased flexibility of joints and of blood vessel walls because of altered protein fibers. The blood vessels have increased “give.” When the patient stands up, blows against a resistance, or carries out any activity that impedes the return of blood to the heart, too much blood collects in the veins, decreasing delivery of blood to the brain.

Both POTS and autonomically mediated syncope are far more prevalent in women than in men. Given the account of the climbing snakes and water snakes, maybe the greater prevalence of these syndromes in women relates also to structural and functional gender differences, such as lower centers of gravity, lower blood pressure, less well developed skeletal muscle below the level of the heart, a larger pool of venous blood in the pelvis, and greater inherent stretchability of blood vessels. I speculate on this later on in the section on apples and pears.

Several years ago I had the opportunity to meet Dr. Lillywhite and ask him whether water snakes when tilted upright faint. He replied that their blood pressure at the level of the head would fall to zero, but he never kept them in this position long enough

to see if they actually lost consciousness.

FAINTING WHILE LECTURING TO AUTONOMICS EXPERTS

In October of 2007, at a combined meeting of the American Autonomic Society and the European Federation of Autonomic Societies took place in Vienna, I was in the audience when a remarkable demonstration of autonomically mediated syncope occurred—the lecturer fainted.

The lecturer was (and still is) an expert on autonomic changes accompanying exercise. When her turn came, she strode to the lectern to give her talk. Soon afterward, though, she paused and then slumped slowly to the floor. Colleagues and I immediately rushed to her aid. She was barely conscious. Initially her pulse was present but almost impalpable. She was pale and sweaty. Her pupils were dilated. After a minute or two of her being supine, her pulse returned and became bounding and full, and about the same time she became alertness and began to speak lucidly. As I recall, her talk was deferred.

Ironically, in 2009 she published an article about sympathetic neural mechanisms in human cardiovascular health and disease, and in the article she wrote:

“Movement from a supine or sitting position to an upright position requires complex adjustments in blood flow and blood pressure, and these adjustments are ultimately coordinated by sympathetic nerves in conjunction with parasympathetic

modulation of heart rate. Without such adjustments, blood flow to the brain would fall below autoregulatory limits, and standing up would consistently cause syncope.”

Postural Tachycardia Syndrome (POTS)

Synopsis:

Mainly young adult women.

Too rapid pulse rate during standing.

Several non-specific associated problems (inability to tolerate prolonged standing, chronic fatigue, faintness, exercise and heat intolerance, headache, neuropathic pain, slowed gastrointestinal movements, chest pain, heart “flip-flops,” tendency to panic)

Variable outlook, can improve.

Not life-threatening.

Patients with the postural tachycardia syndrome (postural orthostatic tachycardia syndrome, POTS) have an excessive increase in pulse rate when they are standing.

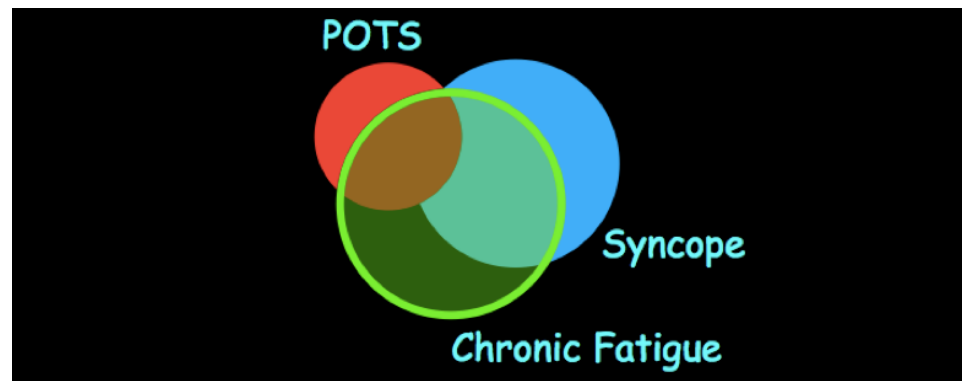
POTS is a syndrome, not a single disease, and can have any of several causes.

Different research groups have different views about the classification of dysautonomias and especially about POTS and chronic orthostatic intolerance. Some investigators view POTS as synonymous with chronic orthostatic intolerance. The condition has features that are also suggestive of hyperdynamic circulation syndrome or “neurasthenia.” The many terms that have been used probably reflect different emphases at different

centers and gaps in knowledge about underlying mechanisms.

POTS patients not only have too rapid a pulse rate when they stand, they also have several other non-specific symptoms.

At least some of these symptoms are thought to reflect increased effects of the catecholamines, norepinephrine or adrenaline, from overactivity of the sympathetic noradrenergic system, the sympathetic adrenergic system, or both.



POTS, autonomically mediated syncope, and chronic fatigue often occur together.

The orthostatic tachycardia usually occurs without orthostatic hypotension. The finding of orthostatic hypotension does not exclude a diagnosis of POTS, however, as delayed orthostatic hypotension can occur in this condition.

In general medical practice, the finding of an excessive increase in heart rate with standing is usually secondary to identifiable problems such as medications or dehydration from chronic illness. It is only when the cause is not readily identified, and

the patient has some of the other complaints discussed below, that the patient is thought to have postural tachycardia syndrome, or POTS.

THE KEY IS THE "S"

The key word in postural tachycardia syndrome is “syndrome.” A syndrome is a set of symptoms that occur together. Merely having a fast pulse rate while standing is not a syndrome, which always involves more than a single symptom or sign.

FATIGUE

Orthostatic intolerance

Heart racing/palpitations/chest pain

"Brain fog"

GI issues (abd. pain, bloating, gastroparesis, nausea)

Chronic pain (fibromyalgia, TMJ, headache)

Exercise intolerance

Delayed orthostatic hypotension/syncope

Sleep abnormalities (non-refreshing, insomnia)

Heat intolerance

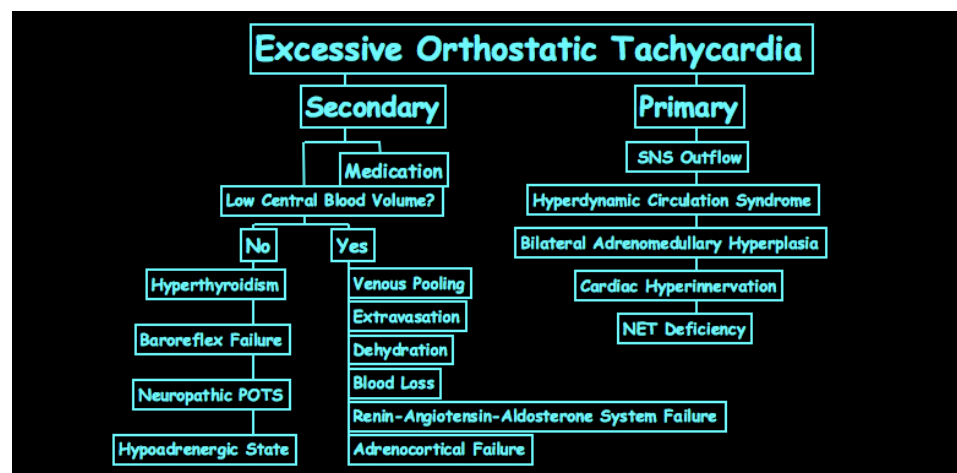
POTS is a syndrome, because it is associated with a variety of symptoms that, when thought of individually, are not specific for any particular disease.

Patients with POTS not only have a rapid pulse rate when they stand up, they also have several other symptoms, such as orthostatic intolerance, chronic fatigue, a tendency to faint, chest pain, pain in the back of the neck or shoulders, headache,

cool, sweaty extremities, heat intolerance, exercise intolerance, palpitations, gastrointestinal complaints (nausea, early satiety, slow gastrointestinal transit, bloating, gastroesophageal reflux, abdominal pain) and neuropsychological complaints such as disturbed sleep, panic, anxiety, depression, “brain fog,” and generalized disability.

The occurrence of a rapid pulse rate when a person stands is necessary but is not sufficient to diagnose POTS.

PRIMARY VS. SECONDARY CAUSES OF POTS



An algorithm for clinical evaluation of excessive orthostatic tachycardia

Trying to identify a specific cause in a particular patient with POTS can be a great challenge to clinicians. There are probably as many causes of a fast pulse rate as there are of a fever, and the typical symptoms of POTS are not specific for

any single disease.

Researchers have thought that usually in POTS, sympathetic nerve traffic to the heart is increased as a compensation. The compensation could be for a decrease in the amount of blood returning to the heart or a decrease in the total peripheral resistance to blood flow when the patient stands up. Either situation could alter information from the baroreceptors to the brain, leading to a reflexive increase in sympathetic noradrenergic system activity directed by the brain.

BLOOD VOLUME AND POTS

There are many causes for a decrease in the amount of blood returning to the heart when a patient is standing. The possibility of blood volume depletion or excessive pooling of blood in the legs during standing up has drawn particular attention. Indeed, low blood volume was noted in the first reported case of POTS. The response to IV infusion of normal saline can be dramatic, at least in the short run.

Dehydration, blood loss, or other causes of decreased blood volume can produce a condition that looks like POTS.

Delayed orthostatic hypotension in POTS is also thought to result from a progressive, exaggerated decline in blood volume during prolonged standing, from leakage of fluid into the tissues through blood vessel walls (extravasation). Consistent with excessive blood pooling in the legs or lower abdomen during orthostasis, inflation of a military anti-shock trousers

(MAST) suit reduces substantially the increase in heart rate in response to orthostasis in patients with POTS.

Low blood volume in turn can result from blood loss, from failure of the bone marrow to make an adequate number of red blood cells, or from failure of hormone systems such as the renin-angiotensin-aldosterone system. Blood volume can fall due to extravasation while a person stands for a prolonged period.

An “effective” low blood volume can occur, when the blood pools excessively in the veins in the pelvis and abdomen after a person stands, such as because of a lack of muscular “tone” in the vein walls. It is possible that a problem with the protein structure of blood vessel walls could lead to POTS. POTS in Ehlers-Danlos syndrome may be an example of such a condition.

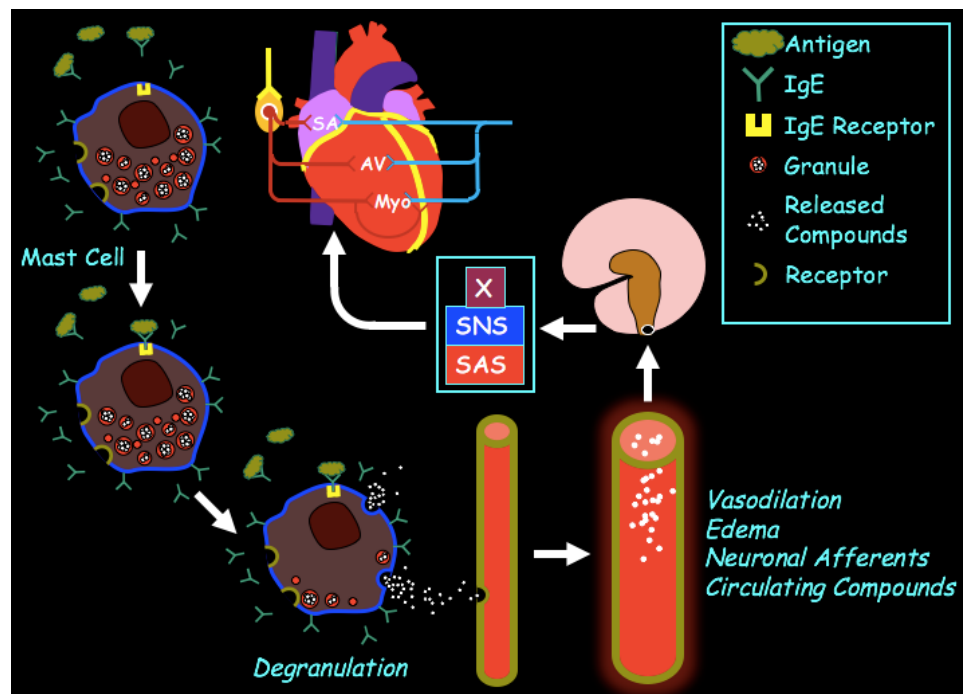
MAST CELL ACTIVATION SYNDROME (MCAS)

Mast cells are a type of immune cells that play key roles in acute allergic responses. They express receptors for IgE, the immune globulin involved with anaphylaxis, as well as receptors for a variety of other chemical messengers.

When activated, mast cells release several compounds, including monoamines such as histamine, serotonin, and dopamine, as well as cytokines such as TNF- α , interleukins, and leukotrienes. Taken together, these compounds exert important effects on the cardiovascular, respiratory, and

gastrointestinal systems and the skin.

In Mast Cell Activation Syndrome (MACS), the mast cells release their chemicals inappropriately or excessively. Symptoms of MACS include flushing, itching, diarrhea, nausea, wheezing, fatigue, brain “fog”, orthostatic intolerance, and fainting reactions.



Concept diagram for how mast cell degranulation may result in orthostatic tachycardia

Mast cells release a protein called tryptase, and MACS patients have high tryptase levels; however, whether the frequency with which POTS patients have elevated tryptase is unknown.

To determine whether a patient with orthostatic intolerance has MACS, it has been proposed that three criteria should be met:

(1) The patient should have symptoms consistent with MACS,

such as repeated episodes of flushing, itching, nasal congestion, coughing, chest tightness, wheezing, abdominal pain, or diarrhea; (2) There should be laboratory evidence of mast cell activation; and (3) there should be improvement of symptoms with the use of medications such as anti-histamines or leukotriene receptor blockers. Cromolyn sodium, which stabilizes mast cells, is also used.

Although patients with Mast Cell Activation Syndrome (MACS) often have symptoms of POTS, the frequency of MACS in POTS is unknown.

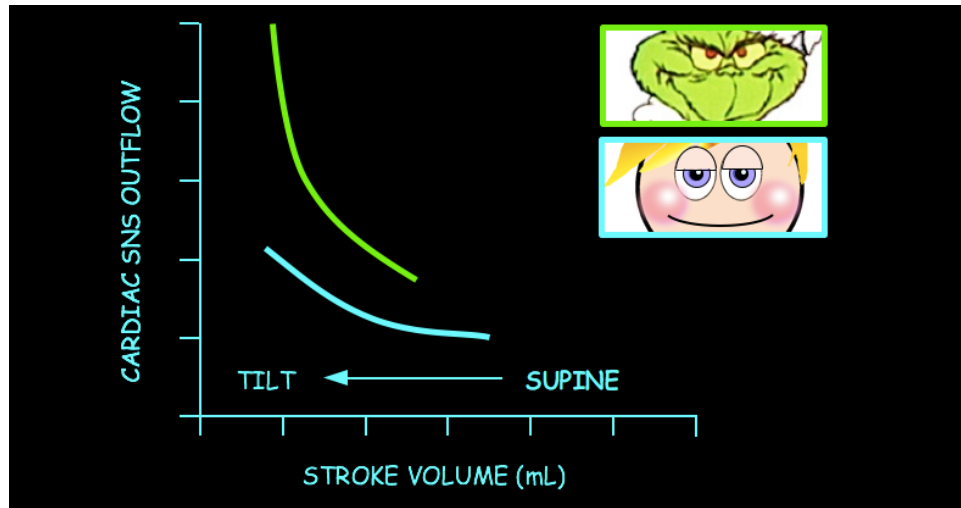
People with inherited high tryptase levels due to an increased copy number of the *TPSAB1* gene have multisystem complaints such as flushing, itching, nausea, diarrhea, chronic pain, joint hypermobility, orthostatic intolerance, and syncope.

MACS, Ehlers-Danlos syndrome, and POTS can occur together. The bases for this triad are poorly understood.

GRINCH SYNDROME

Drs. Qi Fu and Ben Levine, of the University of Texas Southwestern Medical Center in Dallas, came up with a novel name for a type of POTS: “Grinch syndrome.”

“Grinch syndrome,” refers to the Dr. Seuss character who had a heart that was “two sizes too small.” Fu and Levine have proposed that marked tachycardia during orthostasis in Grinch syndrome patients is a compensation for low stroke volume.



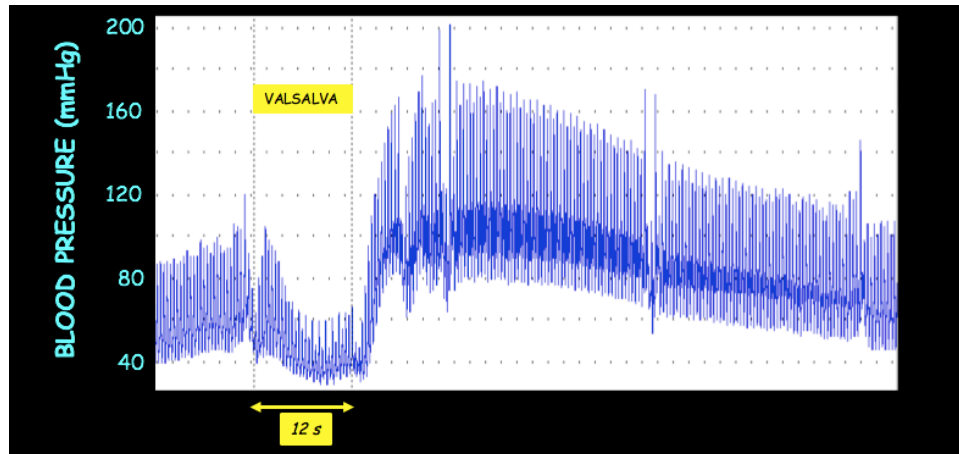
Grinch syndrome is named for the Dr. Seuss character who had a heart “two sizes too small.” Here is how a patient with Grinch syndrome might respond to head-up tilt.

Exercise training has often been helpful in such patients.

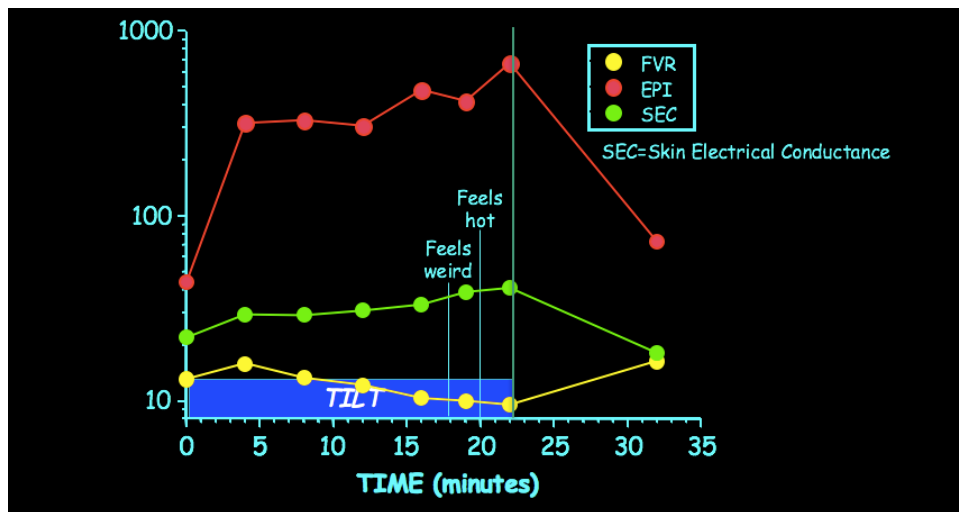
We diagnosed Grinch syndrome in a POTS patient—an adolescent with congenital pectus excavatum and a cardiac stroke index (stroke volume adjusted for body surface area) below the lower limit of normal. The pectus excavatum may have been severe enough to actually limit the growth of his heart. When he performed the Valsalva maneuver, there was a huge, sustained Phase IV overshoot in blood pressure, and when he was tilted head-up on a tilt table, he had an excessive orthostatic increase in the arterial plasma norepinephrine (NE) level, both findings indicating excessive responsiveness of the sympathetic noradrenergic system.

As the tilting proceeded, he had a progressive increase in skin electrical conductance (a measure of sweating). His arterial plasma adrenaline levels continued to increase beyond the

proportionate increase in plasma NE—sympathoadrenal imbalance (SAI).



Dramatic Phase IV overshoot of blood pressure in a patient with POTS and Grinch syndrome. In the same patient there was a marked increase in plasma norepinephrine during tilt-table testing. Both abnormalities indicate excessive sympathetic noradrenergic system responses to stimuli that decrease venous return to the heart.



Sweating and forearm vasodilation before tilt-induced neurally mediate hypotension and syncope.

As the adrenaline level increased, forearm vascular resistance fell. Eventually the patient developed sweating and forearm vasodilation, which preceded neurally mediated hypotension.

NEUROPATHIC POTS

In “partial dysautonomia,” or “neuropathic POTS,” there is thought to be a patchy loss of sympathetic nerves, such as in the legs or splanchnic organs. When the patient stands up, the blood pools in the veins, and less blood returns to the heart, or else the arterioles fail to constrict, and the total resistance to blood flow decreases. In response to either or both of these abnormalities, the sympathetic noradrenergic system supply to the heart is stimulated reflexively.

In “neuropathic POTS,” sympathetic nerves to the heart are thought to be overactive as a compensation for loss of sympathetic nerves elsewhere.

There are other possible causes of decreased total peripheral resistance that might reflexively increase sympathetic noradrenergic system traffic to the heart. For instance, any of several drugs block receptors for norepinephrine in blood vessel walls; other drugs directly relax blood vessel walls. The recent introduction of analyses of skin biopsies for small fiber neuropathy may help refine the diagnosis of neuropathic POTS.

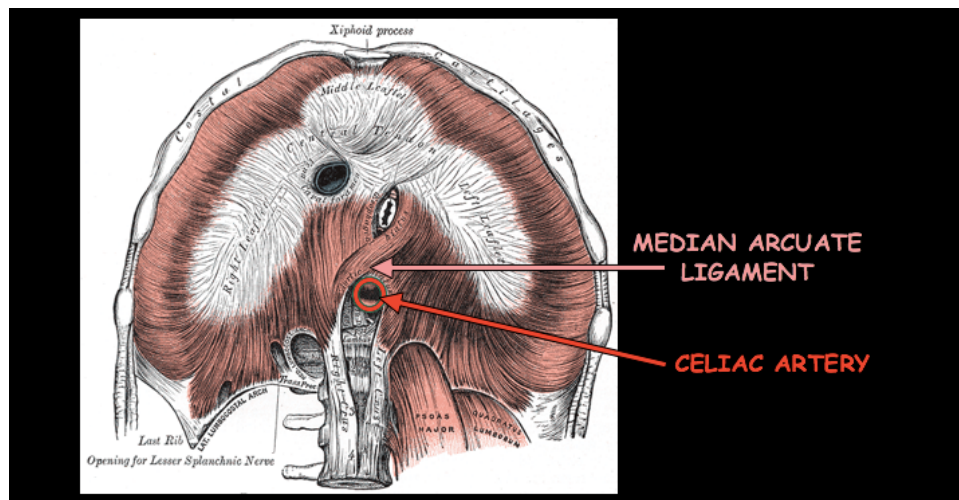
GUT WRENCHING

The median arcuate ligament syndrome (MALS), also called celiac artery compression syndrome, can produce an unusual

form of POTS in which abdominal pain, nausea, and vomiting are prominent clinical features. The patients are thin, because meal ingestion evokes pain.

Hearing an abdominal bruit (a whooshing sound due to turbulent blood flow through a narrowed artery) that is worse at end-expiration can be a clue. Doppler-ultrasound testing in this situation shows increased blood velocity through the narrowed artery. Surgical release of the compression can result in rapid improvement.

Mechanisms by which MALS causes POTS are poorly understood and may result from a combination of hypovolemia, impingement of local autonomic nerves, and distress.

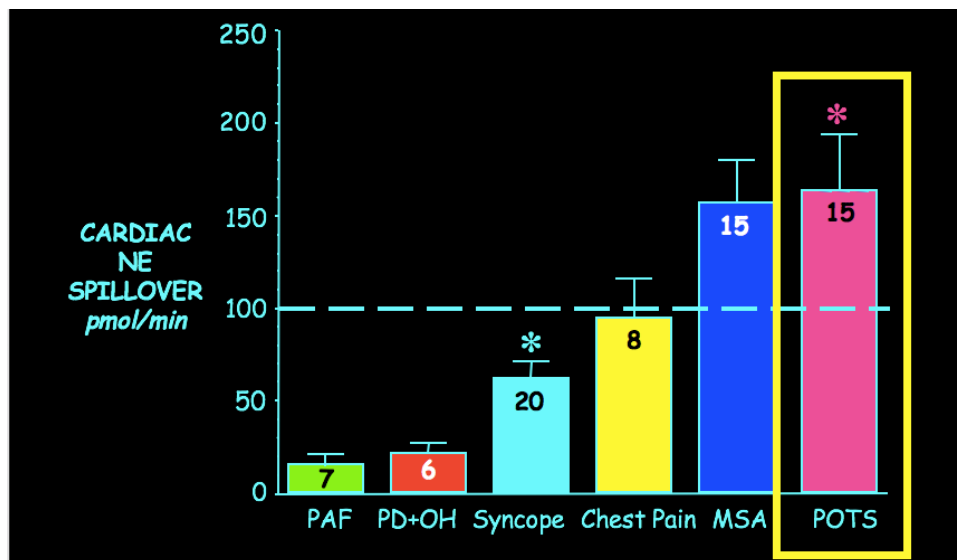


The median arcuate ligament syndrome results from compression of the celiac artery as it passes through the diaphragm.

HYPERADRENERGIC ORTHOSTATIC INTOLERANCE

In “hyperadrenergic orthostatic intolerance,” the problem is thought to be a primary abnormality in the functioning or regulation of the sympathetic noradrenergic or sympathetic adrenergic system.

Patients with POTS often have increased plasma levels of norepinephrine, the chemical messenger of the sympathetic noradrenergic system, especially when they are standing up.



On average, POTS patients have an increased rate of entry of norepinephrine (NE), the chemical messenger of the sympathetic noradrenergic system, into the venous drainage of the heart, even when they are lying down.

According to one suggestion, criteria for diagnosing POTS include an upright plasma norepinephrine (NE) level of 600

pg/mL or more; however, whether increased sympathetic nervous outflows constitute a primary abnormality or compensatory response usually is unknown in an individual patient.

Even when POTS patients are supine, the rate of spillover of NE into the venous drainage of the heart is statistically increased.

In a related syndrome, called the hyperdynamic circulation syndrome, the patients have a fast pulse rate all the time, variable high blood pressure, increased heart rate responses to the drug, isoproterenol, and increased plasma norepinephrine and adrenaline levels at rest and during provocative maneuvers. β -Adrenoceptor blockers such as propranolol or benzodiazepines such as diazepam improve the syndrome. It is unclear whether patients with this syndrome have an increased frequency of later development of established hypertension. Episodes of fast pulse rate and increased blood pressure can be associated with blotchy flushing of the face, neck, and upper chest.

“Neurasthenia” a term introduced in the late 1860s, refers to a syndrome initially described in Civil War soldiers. Also called neurocirculatory asthenia, the syndrome consists of a large number of symptoms, including breathlessness, palpitations, chest pain, dizziness, shortness of breath on exertion, fatigue, excessive sweating, trembling, flushing, dry mouth, numbness and tingling feelings, irritability, and exercise intolerance.

Most research about neurocirculatory asthenia has been conducted in Russia. Western cardiovascular researchers rarely

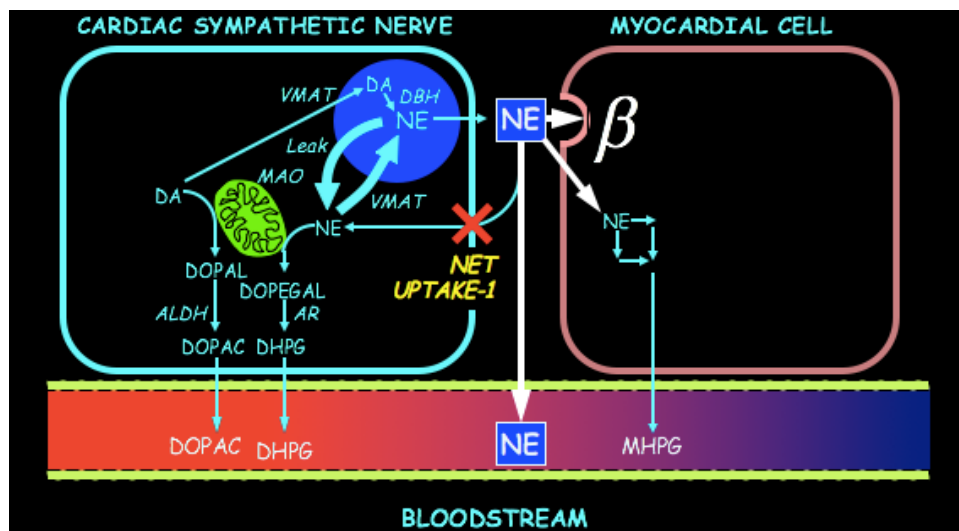
use this term. The symptoms resemble those in POTS, and as in POTS the multiplicity of symptoms contrasts with a relative lack of signs, which all are non-specific—relatively fast pulse rate, relatively rapid breathing, facial and neck flushing, slight tremor, sweaty palms, a “functional” heart murmur, and hyperactive knee jerk reflexes, with generally normal resting blood pressure. Just as in POTS or the hyperdynamic circulation syndrome, in neurasthenia injections of adrenaline can evoke these symptoms. β -Adrenoceptor blockers often normalize the cardiovascular findings without affecting the other symptoms and signs. Drugs such as caffeine can evoke fast pulse rate, increased ventilation, tremor, and sweatiness in patients with neurocirculatory asthenia.

In inappropriate sinus tachycardia, the heart rate is increased markedly from normal, even under resting conditions. Radiofrequency ablation of the sinus node, the heart’s pacemaker area, is considered for patients with inappropriate sinus tachycardia who are resistant to treatment with medications. Radiofrequency ablation does not usually improve the condition of patients with POTS.

Failure of the arterial baroreflex can produce a hyperadrenergic condition, because the patient cannot buffer the pressor effects of increases in sympathetic noradrenergic and adrenergic system outflows; however, one would not expect excessive orthostatic tachycardia in a patient with baroreflex failure. Baroreflex failure is discussed separately.

THE NET RESULT

The cell membrane norepinephrine transporter (NET) plays a key role in inactivating norepinephrine. Normally, about 90% of the norepinephrine released from sympathetic nerve terminals is recycled by being taken back up into the nerve terminals. When the NET is underactive, more norepinephrine is delivered to its receptors in the heart and blood vessel walls for a given amount of norepinephrine release, producing an exaggerated increase in pulse rate and blood pressure when the sympathetic noradrenergic system is activated. One family has been described in which POTS is inherited because of a mutation of the gene encoding the NET.



In NET deficiency, for the same amount of norepinephrine (NE) release there is excessive delivery of NE to beta-adrenoceptors on myocardial cells.

NET deficiency is a very rare cause of POTS.

Although NET deficiency is an extremely rare cause of POTS, it is important scientifically and, in a way, culturally. If POTS can have a genetic cause, then it cannot only reflect a psychiatric or psychosomatic disorder. The various symptoms and signs and continual life challenges of POTS from NET deficiency are essentially the same as those in much more frequent forms of POTS, illustrating that disorders of regulation such as POTS can arise from any of multiple causes. Different determinants can lead to essentially the same syndrome, but the syndrome is real.

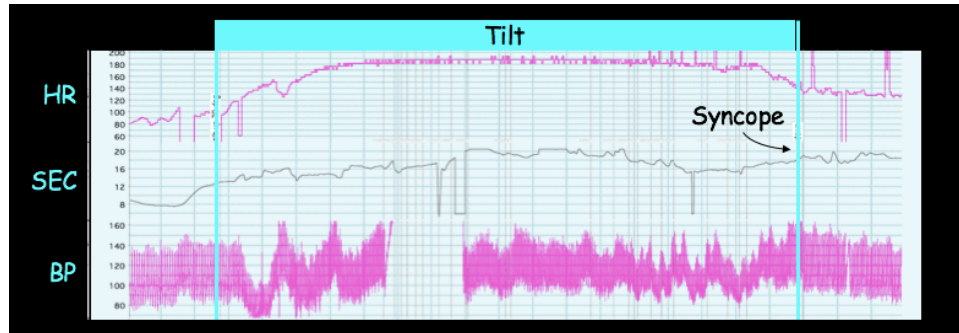
I've always been puzzled about why decreased NET activity should produce orthostatic intolerance, but I know from my own experience that it does. Once as part of my research I took a dose of 125 mg of desipramine, a drug that temporarily blocks the NET. For hours afterward I had orthostatic intolerance, tachycardia, and brain “fog.” According to my team, I also had dysphoria—sour mood, or a state of unease or generalized dissatisfaction with life. But maybe that's me anyway.

POTS WITH AUTONOMICALLY MEDIATED SYNCOPE

Although POTS and frequent fainting (autonomically mediated syncope, neurocardiogenic syncope, reflex syncope) are considered to be different forms of chronic orthostatic intolerance, when POTS patients are subjected to tilt table testing, a substantial minority have fainting reactions.

When they do, they have the same pattern of “sympathoadrenal imbalance” as found in patients with fainting who do not have

POTS. In sympathoadrenal imbalance, there is a dissociation between plasma adrenaline levels, an index of sympathetic adrenergic system (SAS) activity, and plasma norepinephrine levels, an index of sympathetic noradrenergic system (SNS) activity.



Polygraphic recording demonstrating excessive orthostatic tachycardia, sweating (measured by skin electrical conductance, or SEC), and blood pressure variability followed by syncope.

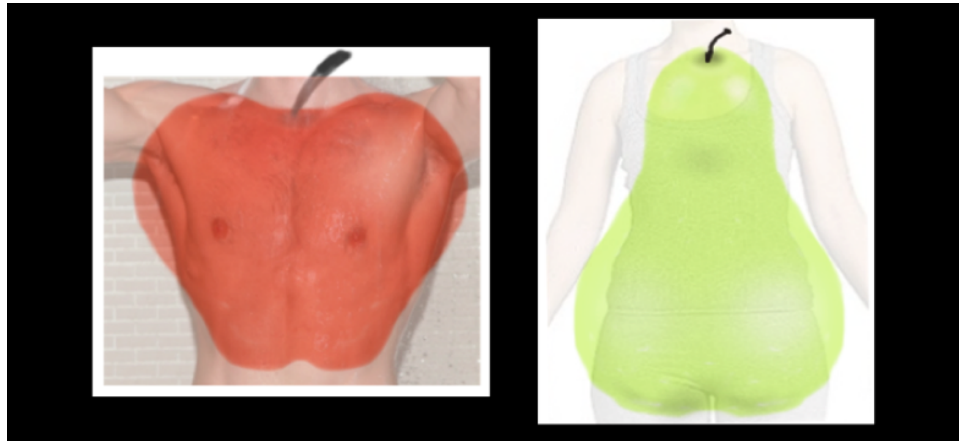
COMPARING APPLES WITH PEARS

Chronic orthostatic intolerance syndromes such as POTS are much more common in women than in men. The basis for this difference remains poorly understood.

One possibility is the body shapes of men and women, as a result of hormonal differences throughout development. In general, a man's body is shaped like an apple, with broad shoulders, while a woman's body is shaped like a pear, with broad hips.

It seems reasonable to speculate that during orthostasis there would be more of a tendency of blood to pool in the abdomen and pelvis in women than in men. If so, then for the same

amount of abnormal increase in the capacitance of veins, there would be a more severe decrease in venous return to the heart in women and consequently more reflexive recruitment of sympathetic noradrenergic outflows, resulting in a larger tachycardia response.



Male and female physiognomies— “apples” and “pears”

During orthostatic stress, whether induced by tilt table testing or lower body negative pressure, women do have more blood pooling in the pelvic region than do men. This is probably because women have anastomoses between uterine and ovarian arteries and large plexuses of veins around the uterus, ovaries, and vagina.

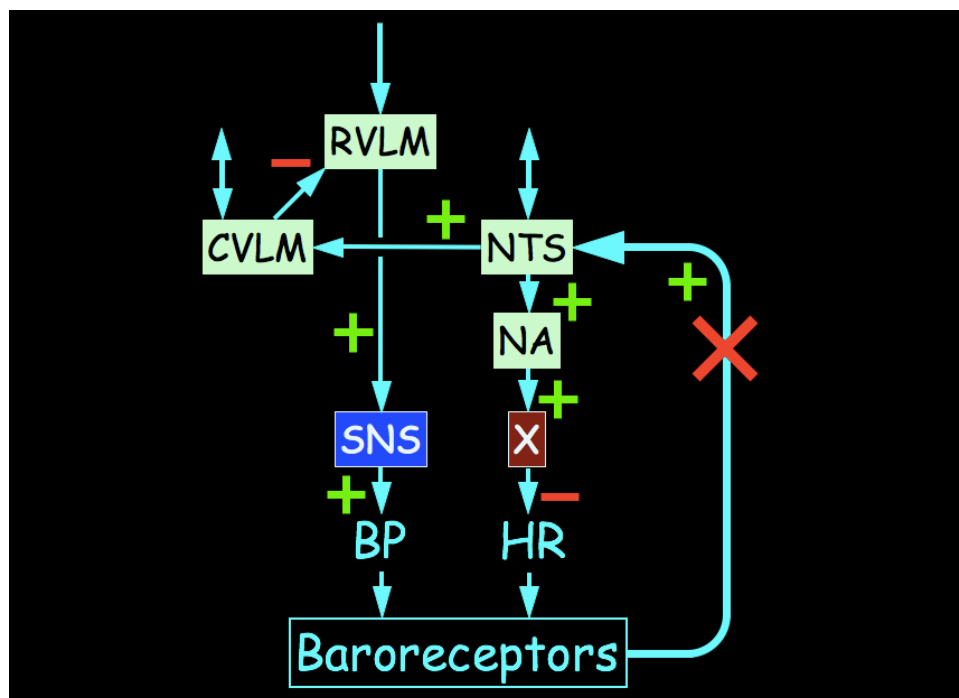
People with Klinefelter syndrome (genotypically XXY) are phenotypically men, because they have a Y chromosome, but they are feminized because they have two XX chromosomes. They have broad hips and narrow shoulders. POTS has been reported in a patient with this syndrome.

This physiognomic notion is probably over-simplistic. Among other things, it does not explain easily why chronic fatigue

syndrome, autonomically mediated syncope, migraine, temperomandibular joint disorder, Sjogren's syndrome, and fibromyalgia—which often overlap—are also all more common in women than men.

Baroreflex Failure

In arterial baroreflex failure, the brain does not respond appropriately to information from the cardiovascular system, and the sympathetic noradrenergic system is activated inappropriately because of release from baroreceptor restraint.



Arterial baroreflex failure from an afferent lesion

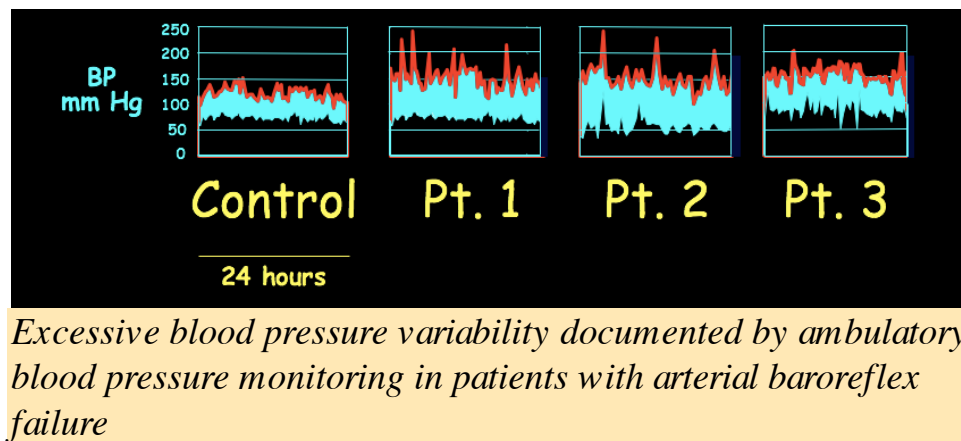
In baroreflex-cardiovagal failure, the heart rate does not increase when the person stands up or is tilted. This helps distinguish arterial baroreflex failure from POTS as a cause of

chronic orthostatic intolerance.

Failure of the arterial baroreflex can produce orthostatic intolerance.

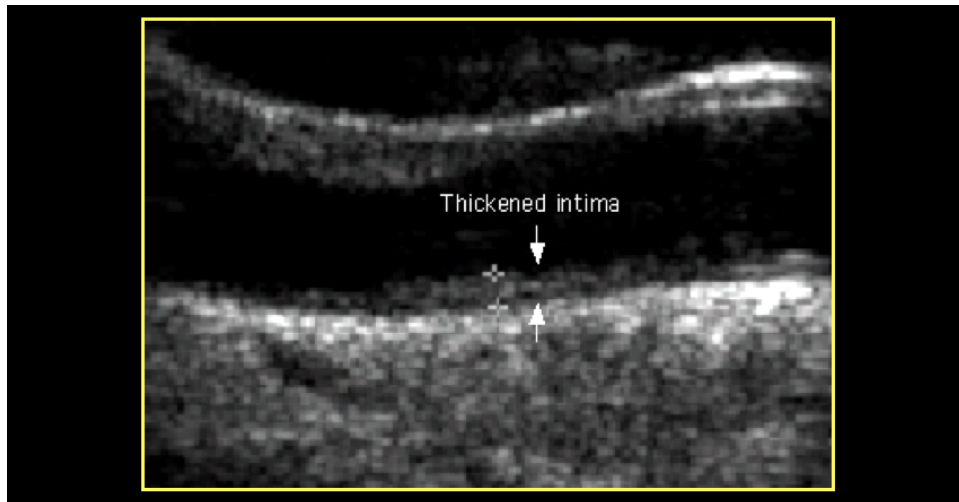
Orthostatic intolerance in baroreflex failure is associated with large swings in blood pressure because of the inability of the baroreflexes to keep the blood pressure in check. There are episodes of extreme high blood pressure and fast pulse rate. Because of this failure, relatively minor stimuli can produce large increases in the activity of the sympathetic noradrenergic system.

Arterial baroreflex failure can result from tumors or neurosurgery that involve the dorsal medulla. Baroreflex failure also is a common correlate of congestive heart failure.



Several years ago Dr. Yehonatan Sharabi, then a Clinical Fellow in our Section, noted that a group of patients with labile blood pressure had a remote history of neck radiation therapy,

such as to treat a lymphoma. The disease itself was gone. He hypothesized—correctly—that baroreflex failure linked neck irradiation in the distant past with cardiovascular instability years later.



Atherosclerotic intimal wall thickening in a patient with arterial baroreflex failure years after neck irradiation

Radiation therapy tends to accelerate hardening of the arteries (arteriosclerosis) in the irradiated area. The baroreceptors are concentrated in the carotid sinus, where the common carotid artery splits in the neck into the internal carotid artery, which supplies blood to the brain, and the external carotid artery, which supplies blood to the face and scalp. The baroreceptors are distortion receptors. If they were encased in a rigidified carotid sinus, such as due to arteriosclerosis after neck irradiation, then arterial baroreflex failure could result. Because of the “debuffering” the blood pressure is allowed to increase and decrease excessively.

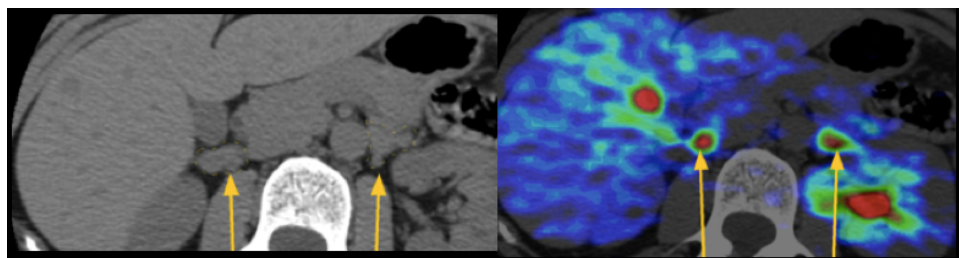
Baroreflex failure is often very difficult to treat. Some patients

have improvement with clonidine. A carotid sinus stimulator that could be switched on and off when needed could be very helpful, but this hasn't been studied.

"Pseudopheo"

Pheochromocytomas (pheos) are rare. Most patients who undergo a diagnostic workup for a pheo prove not to harbor the tumor. The term, "pseudopheochromocytoma," or "pseudopheo," refers to a condition in which the patient has episodes of severe high blood pressure and symptoms suggestive of a pheo, but the patient doesn't actually have a pheo. Sometimes pseudopheo overlaps clinically with orthostatic intolerance syndromes such as arterial baroreflex failure or postural tachycardia syndrome.

Patients with pseudopheo have a pattern of normal sympathetic noradrenergic system outflow, sympathetic adrenergic activation, and augmented adrenoceptor-mediated cardiovascular responses to released catecholamines.



CT and ^{18}F -dopamine scans in a patient with pseudopheo. The arrows point to enlarged adrenal medullas.

Glucagon injection into pseudopheo patients produces a large increase in plasma adrenaline levels. This is not seen in pheo

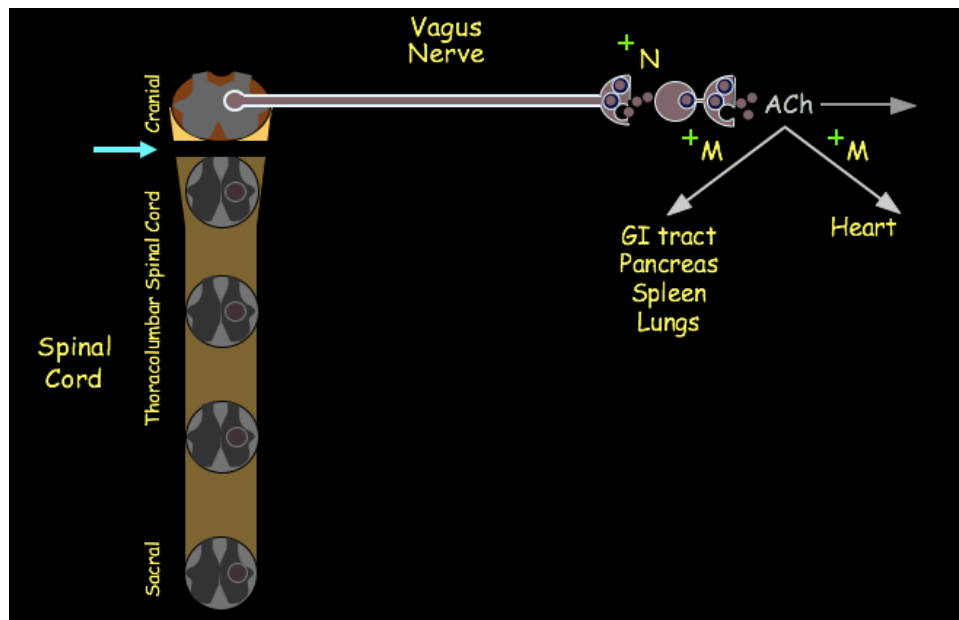
patients or healthy volunteers. Glucagon stimulation testing might therefore be considered in the diagnostic evaluation; however, the sensitivity and specificity of the testing have not been established.

I know of a case of pseudopheo with bilateral adrenomedullary hyperplasia who had marked improvement after unilateral adrenalectomy with contralateral selective adrenal medullectomy.

SPINAL CORD TRANSECTION

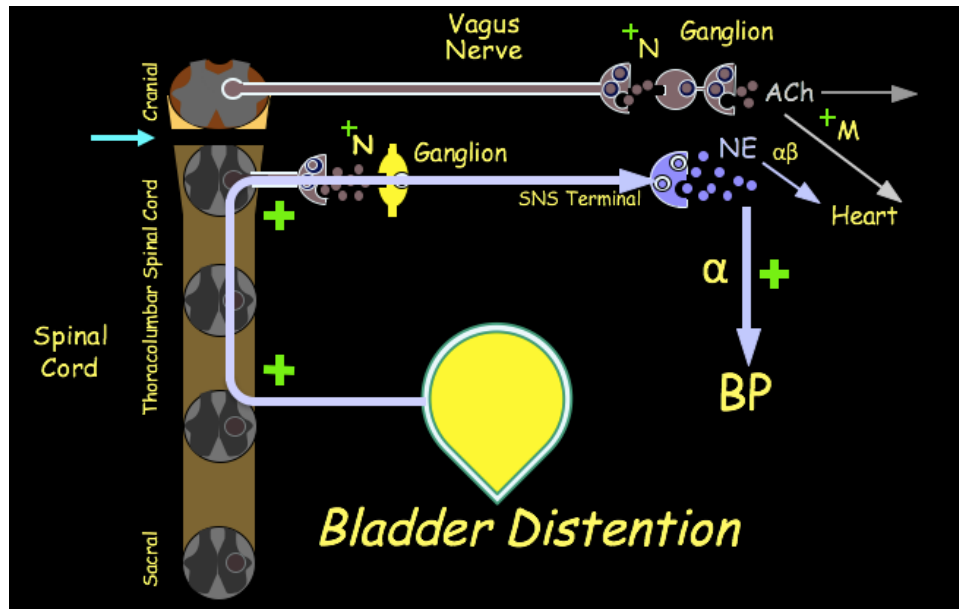
Traumatic accidents that cut the spinal cord (spinal cord transection) results in a particular form of dysautonomia.

The vagus nerve is derived from the brainstem, above the level of spinal cord transection. Spinal cord transection disrupts the pathways descending from the central autonomic network to the sympathetic and the sacral parasympathetic nerves.



Spinal cord transection does not affect the vagus nerve but disconnects the sympathetic nerves and the sacral parasympathetic nerves from the brain.

In patients with spinal cord transection, the nervous connections between the autonomic pre-ganglionic neurons in the



In patients with spinal cord transection, distention of the urinary bladder (or the rectum) can evoke a paroxysmal increase in blood pressure.

intermediolateral columns of the spinal cord and the ganglia and post-ganglionic neurons remain intact. This sets the stage for a phenomenon called “autonomic dysreflexia.”

When the urinary bladder is distended, via a spinal reflex sympathetic noradrenergic outflow to the cardiovascular system increases. Because of the disruption of the baroreflex, there is no buffering of the increase in blood pressure. In patients with spinal cord transection, distention of the urinary bladder or of the rectum can evoke paroxysmal hypertension.

STROKE

Stroke from intra-cranial bleeding (intracerebral hemorrhage or subarachnoid hemorrhage) is associated with a high frequency of electrocardiographic abnormalities. The most common of these is prolongation of the QTc interval. Large, inverted T waves and U waves also occur.




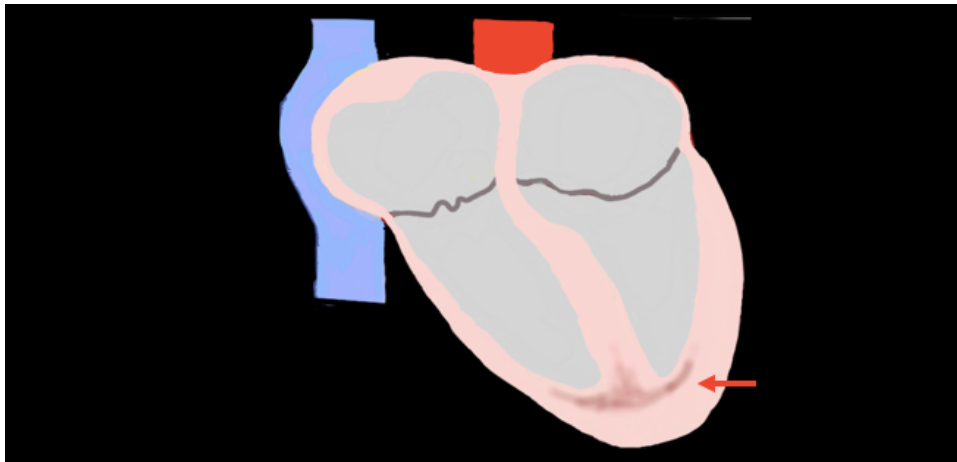
TABLE 1 ECG Findings in 150 Acute Stroke Patients and 150 Age- and Sex-Matched Controls

Finding	Cerebral thrombosis	Stroke, indeterminate etiology	Subarachnoid hemorrhage	Cerebral embolus	Intracerebral hemorrhage	Stroke, overall	Controls
Normal	7 (14%)	4 (11%)	0 (0%)	0 (0%)	1 (6%)	12 (8%)	53 (35%)
Abnormal	42 (86%)	34 (89%)	28 (100%)	19 (100%)	15 (94%)	138 (92%)	97 (65%)†††
Prolonged QT	18 (37%)	15 (39%)	20 (71%)**	7 (37%)	8 (50%)	68 (45%)	18 (12%)†††
T wave inversion	12 (24%)	14 (37%)	7 (25%)	4 (21%)	6 (38%)	43 (29%)	32 (21%)
U waves	13 (27%)	9 (24%)	9 (32%)	4 (21%)	7 (44%)	42 (28%)	14 (9%)†††
Increased HR	7 (14%)	10 (26%)	10 (36%)	8 (42%)	7 (44%)	42 (28%)	12 (8%)†††
ST depression	12 (24%)	12 (32%)	8 (11%)	5 (26%)	4 (25%)	41 (27%)	15 (10%)†††
LVH	12 (24%)	10 (26%)	7 (25%)	3 (16%)	7 (44%)	39 (26%)	18 (12%)††
Q waves	11 (22%)	6 (16%)	6 (21%)	4 (21%)	3 (19%)	30 (20%)	14 (9%)††
Atrial fib.	0 (0%)	8 (21%)	3 (11%)	9 (47%)***	1 (6%)	21 (14%)	6 (4%)††

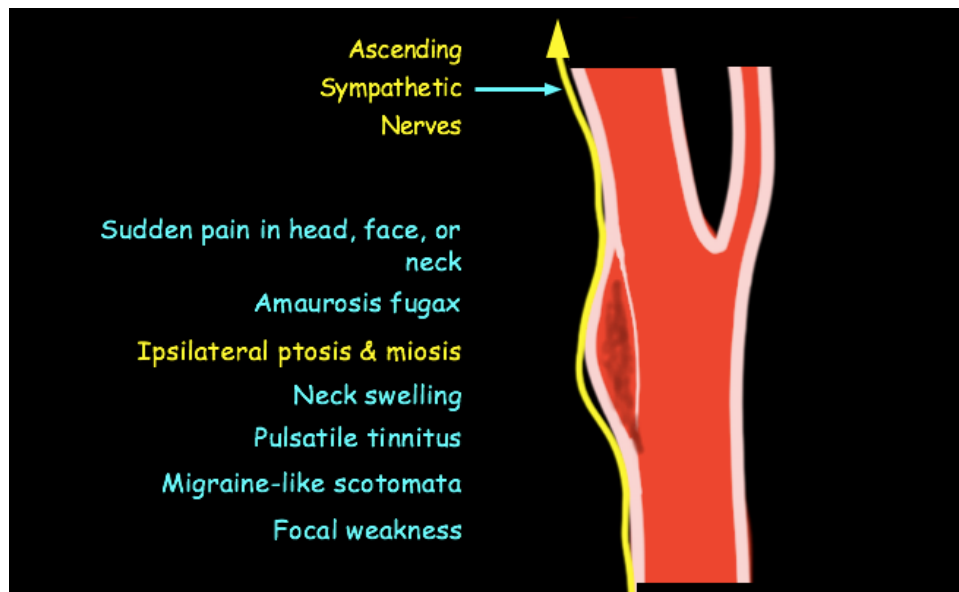
Acute stroke is associated with several EKG abnormalities. The most common new abnormality at the time of a stroke is QTc prolongation, especially in stroke from intra-cranial bleeding.

These EKG abnormalities are also associated with elevations of cardiac-specific enzymes and with subendocardial necrosis. It seems likely that this reflects substantial sympathetic noradrenergic and adrenergic stimulation, as in stress cardiopathy.

Dissection of the carotid artery manifests with a syndrome that in some ways resembles acute stroke, with sudden pain in the face or neck, amaurosis fugax (transient, painless loss of



Subendocardial myocardial infarction occurs in stroke from intra-cranial bleeding.



Dissection of the carotid artery produces a distinctive syndrome that includes ipsilateral ptosis and miosis from interference with ascending traffic in sympathetic nerves.

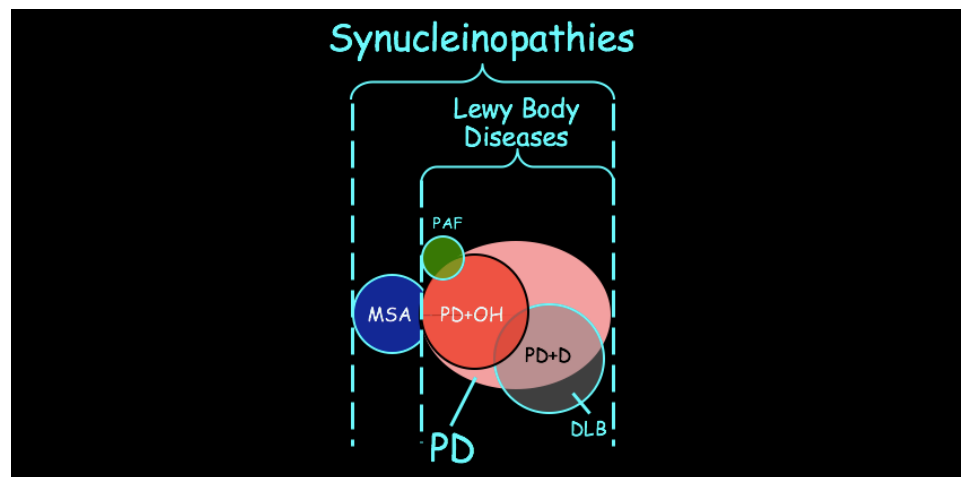
vision), and focal weakness. This syndrome also can include neck swelling, pulsatile tinnitus (ringing in the ears), and scotomata (bright perceived flashes) as in migraine.

CHRONIC AUTONOMIC FAILURE

Autonomic Synucleinopathies

Neurologists have recognized three forms of primary chronic autonomic failure—pure autonomic failure (PAF), multiple system atrophy (MSA), and autonomic failure in the setting of Parkinson’s disease (PD).

Now it is known that all three diseases come under the umbrella of “synucleinopathies,” meaning that they all involve abnormal deposits of the protein, alpha-synuclein.

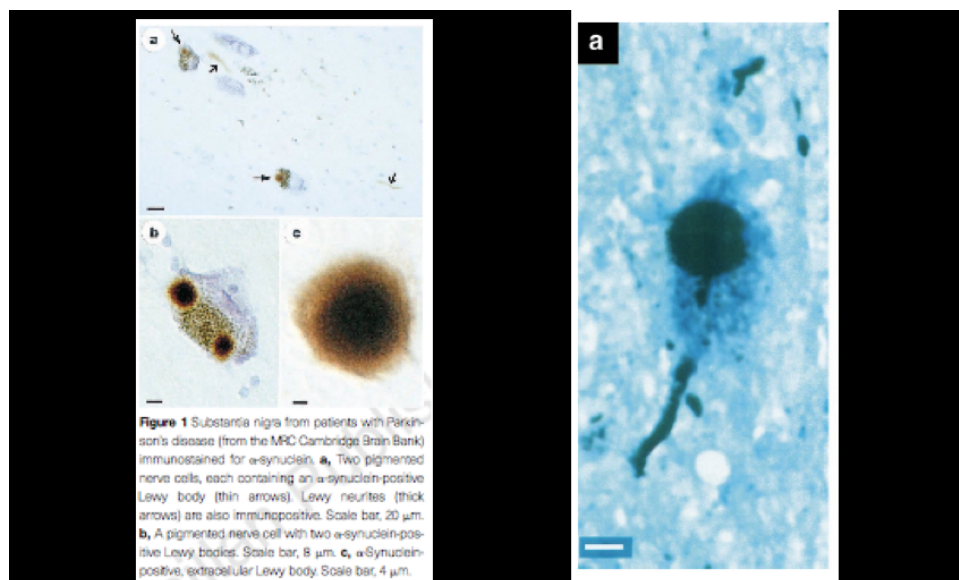


Multiple system atrophy (MSA), pure autonomic failure (PAF), and Parkinson’s disease with orthostatic hypotension (PD+OH), are now considered to be forms of autonomic synucleinopathy.

The alpha-synuclein story is relatively new. In 1997 an international team of researchers reported the first identification of a genetic cause of PD—mutation of the gene encoding alpha-synuclein—in a rare Greek-Italian-American family in which

PD was transmitted as an autosomal dominant trait, meaning that one-half of the family members, whether men or women, had PD and one-half didn't.

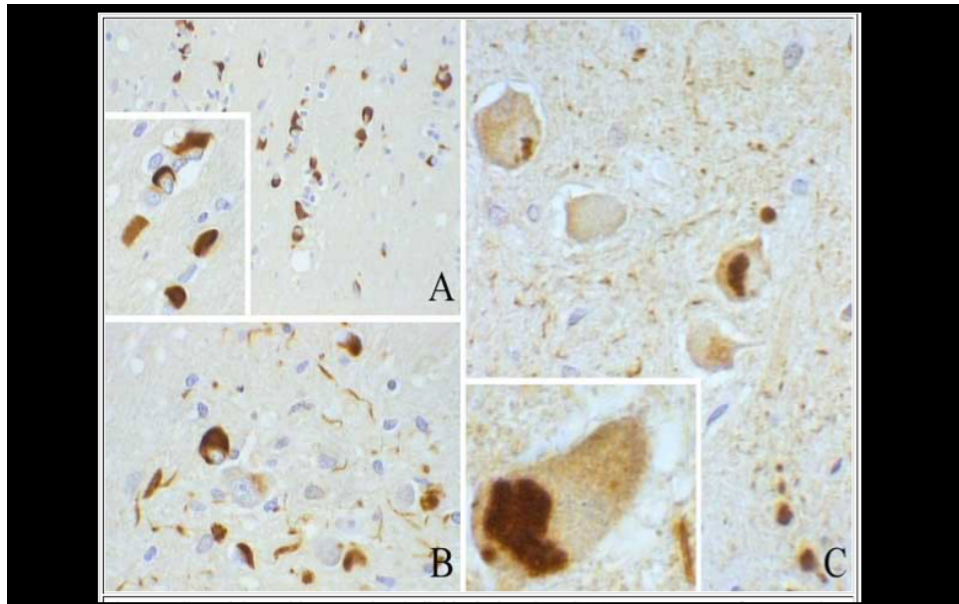
This was an important scientific discovery, but since only one family was involved, it was unclear whether the new information would apply to PD as a whole. In the same year, however, it was found that Lewy bodies, a pathologic hallmark of PD, contain abundant precipitated alpha-synuclein. That is, even sporadic PD was found to involve an abnormality of alpha-synuclein.



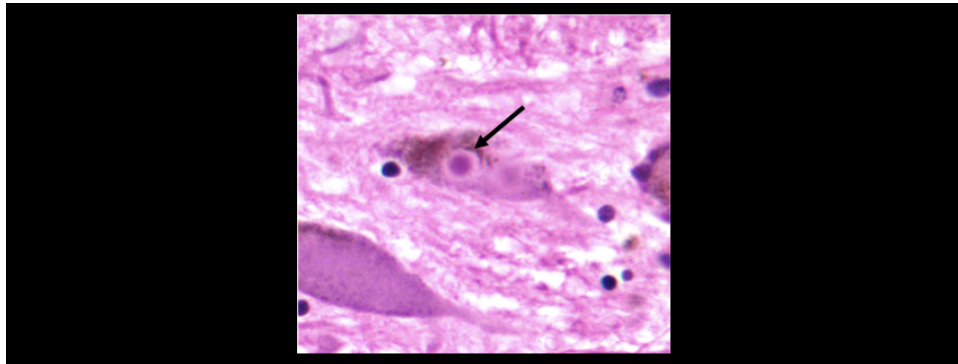
Lewy bodies contain abundant precipitates of alpha-synuclein.

Multiple system atrophy (MSA) was also found to involve alpha-synuclein deposits. In MSA, the deposits are in glial cells, which are helper cells that are not neurons. The deposits of alpha-synuclein were in the cytoplasm of the glial cells, in the form of glial cytoplasmic inclusions (GCIs). MSA of both

the parkinsonian and cerebellar types are characterized by GCIs.



Glial cytoplasmic inclusions are thought to be a neuropathologic hallmark of multiple system atrophy



A Lewy body in the brainstem of a patient with pure autonomic failure.

Then it was found that PAF, the third form of primary chronic autonomic failure, also involves Lewy bodies, both in the brainstem and in sympathetic ganglia.

The idea evolved rapidly that the primary chronic autonomic failure syndromes are in a family of synucleinopathies. Together they are called autonomic synucleinopathies.

About 30-40% of patients with Parkinson's disease have orthostatic hypotension, a fall in blood pressure every time they stand up. This subgroup has been designated "PD+OH." A substantial proportion of PD patients have dementia—PD+D, which overlaps with a condition called dementia with Lewy bodies (DLB), or Lewy body dementia. Most PD patients and at least some PAF patients eventually develop dementia.

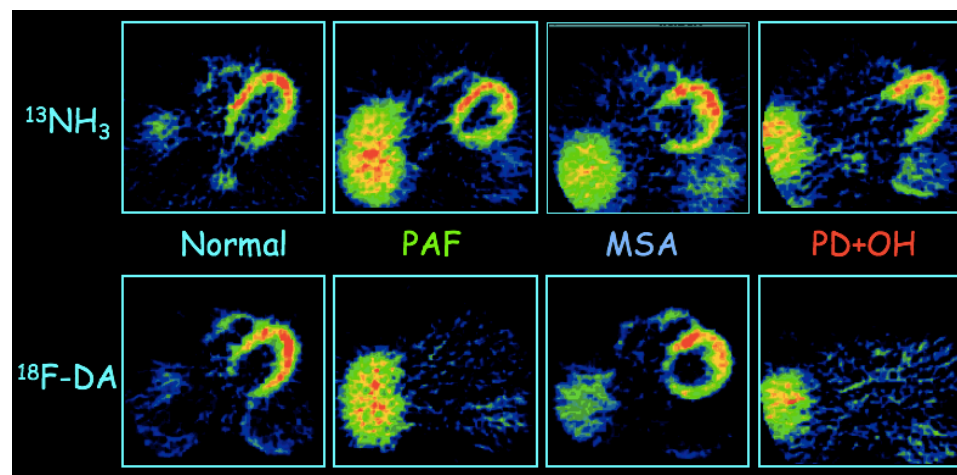
	AAG	PAF	MSA _p	MSA _c	PD+OH
Autonomic Pre-ganglionic					
Autonomic Ganglionic					
Autonomic Post-ganglionic					
Parkinsonism					
Cerebellar, Pyramidal, or Both					

Distinctions among primary chronic autonomic failure syndromes.

MSA, PAF, and PD+OH patients typically have failure of regulation of the sympathetic noradrenergic system by the arterial baroreflex. When they perform the Valsalva maneuver, they have abnormal beat-to-beat blood pressure responses in Phases II and IV. In a patient with orthostatic hypotension,

identifying these abnormalities helps establish a diagnosis of sympathetic neurocirculatory failure but does not distinguish among the three forms of primary chronic autonomic failure.

MSA is sub-classified into parkinsonian and cerebellar forms (MSA-P and MSA-C). MSA-P can be very difficult to separate from PD+OH by clinical symptoms or signs. In general, MSA patients do not have much improvement in their movement disorder when they receive levodopa treatment; however, some do. MSA progresses at a faster rate on average than does PD+OH.



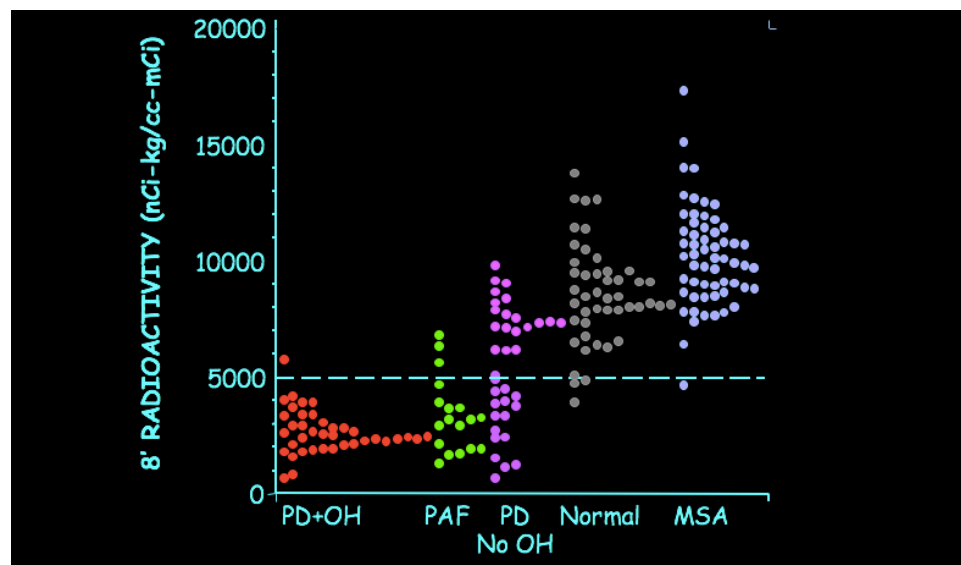
Cardiac sympathetic neuroimaging findings in autonomic synucleinopathies. PAF and PD+OH patients have evidence for loss of cardiac sympathetic nerves, and while most MSA patients have evidence for intact cardiac sympathetic innervation.

Virtually all MSA patients have OH, while only a minority of PD patients have OH. Urinary incontinence is common in both MSA-P and PD+OH, but urinary retention is more closely associated with MSA-P, while urinary frequency

and urgency is common in PD+OH.

PD is much more prevalent than is MSA. This means that a patient with parkinsonism and OH could have either disease.

A powerful way to distinguish MSA-P from PD+OH is cardiac sympathetic neuroimaging, such as by ^{123}I -MIBG SPECT scanning or ^{18}F -dopamine PET scanning.

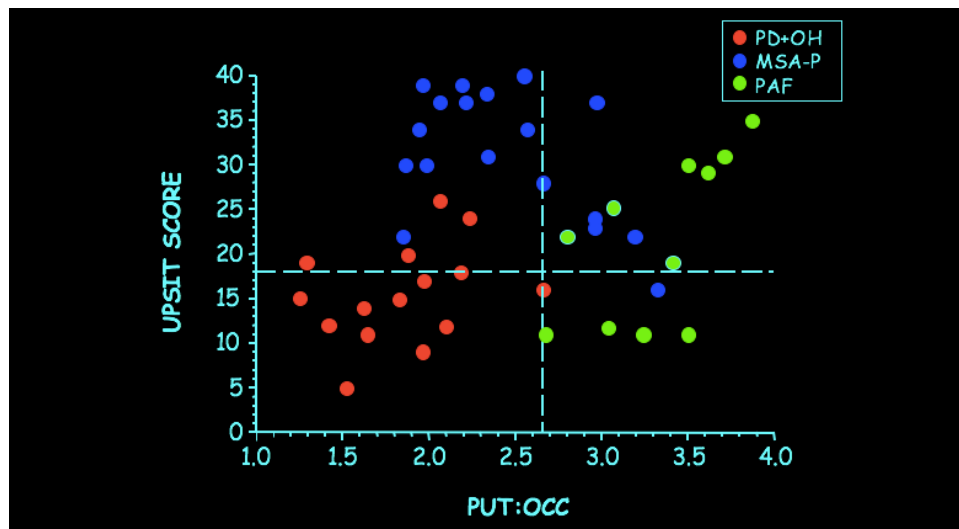


All PD+OH patients (in red) have evidence for cardiac sympathetic denervation, whereas most MSA patients (in blue) have evidence for intact cardiac sympathetic innervation. The dashed line indicates 2 standards deviations below the normal mean.

All PD+OH patients have evidence for a loss of sympathetic noradrenergic nerves in the heart, whereas most MSA-P patients have intact sympathetic noradrenergic innervation. A minority of MSA patients do have evidence for a loss of cardiac sympathetic nerves; however, in a patient with MSA-P vs. PD+OH, the finding of normal cardiac sympathetic innervation

excludes PD+OH.

Another valuable clinical laboratory test in the differential diagnosis of PD+OH vs. MSA-P is assessment of the sense of smell, such as by the University of Pennsylvania Smell Identification Test (UPSIT). Most patients with PD+OH are anosmic. That is, the UPSIT score is 18 or less out of 40.

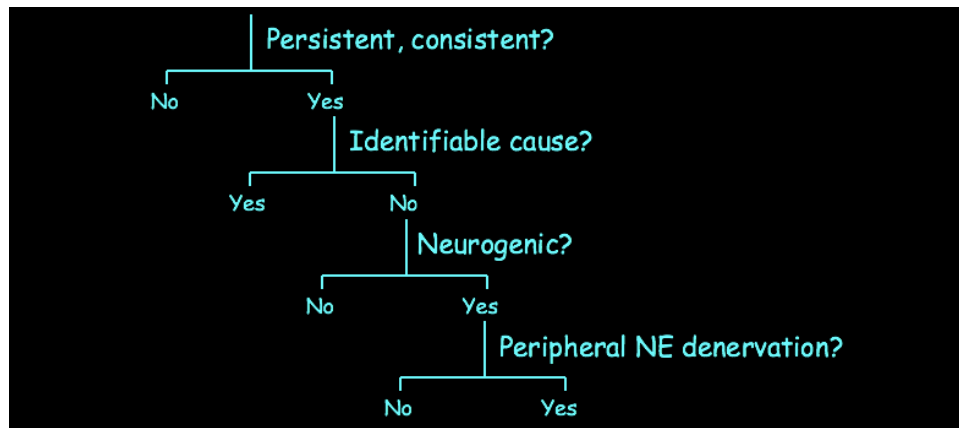


Most PD+OH patients have anosmia according to the UPSIT, whereas most MSA-P patients do not. Both PD+OH and MSA-P involve striatal dopaminergic neurodegeneration, as indicated by a low putamen:occipital cortex (PUT:OCC) ratio of ^{18}F -DOPA-derived radioactivity.

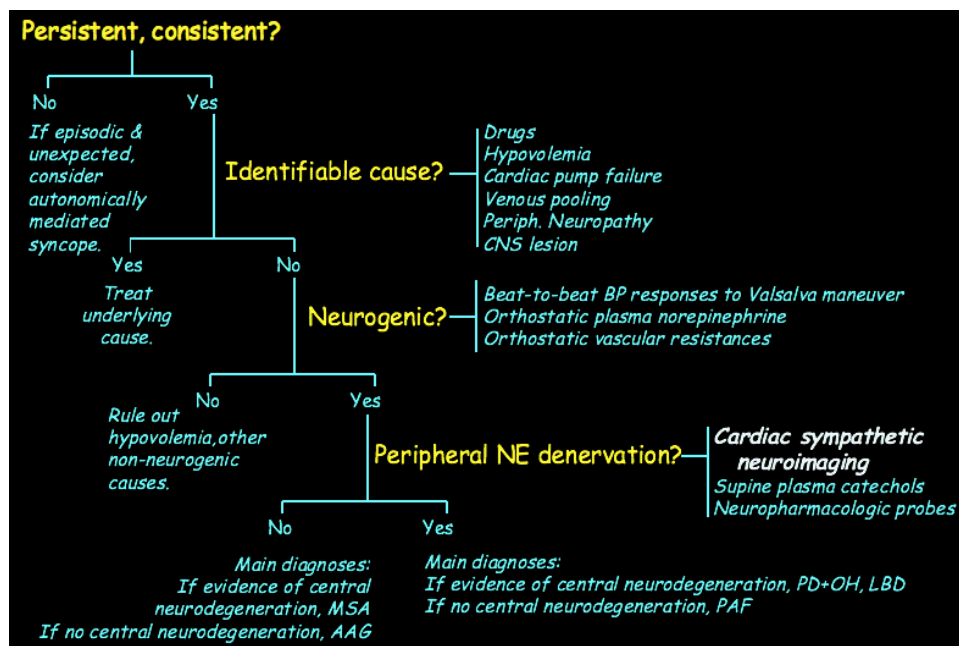
In contrast, many MSA-P patients have normal or only slightly to moderately decreased sense of smell. In a patient with parkinsonism and neurogenic orthostatic hypotension, the finding of normal sense of smell on the UPSIT favors a diagnosis of MSA-P over PD+OH.

In the evaluation of a patient with possible primary chronic

autonomic failure manifesting with orthostatic hypotension, I use a 4-step algorithm.



Four-step approach to the evaluation of orthostatic hypotension.



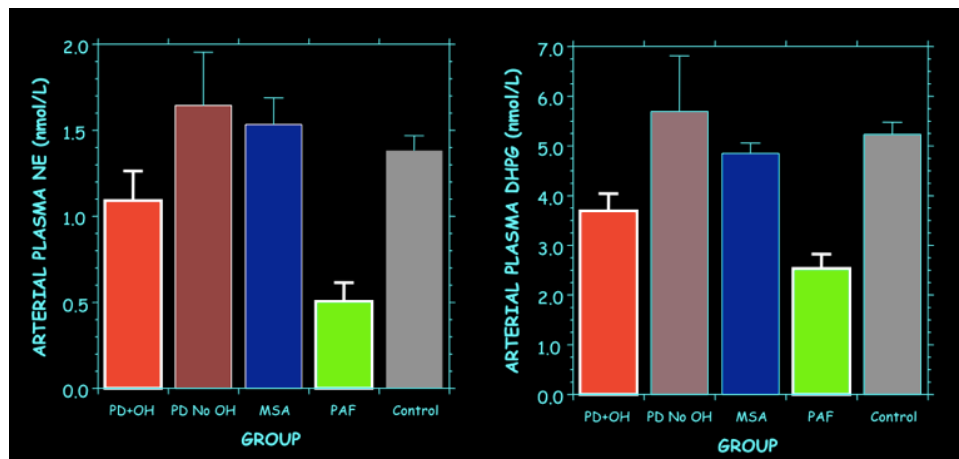
More detailed algorithmic approach to evaluation of orthostatic hypotension.

First, orthostatic hypotension from primary chronic autonomic

failure is a persistent, consistent finding. The patient may not always have symptoms of low blood pressure while standing, but the blood pressure always falls.

Second, in order to diagnose primary chronic autonomic failure, secondary causes such as drugs and diabetes must be excluded.

Third, the orthostatic hypotension should be confirmed to be neurogenic. One way to do this is by assessing the beat-to-beat blood pressure responses to the Valsalva maneuver.



Among patients with orthostatic hypotension, PD patients have somewhat decreased and PAF patients more clearly decreased plasma norepinephrine (NE) and dihydroxyphenylglycol (DHPG) levels.

Sympathetic noradrenergic innervation is generally intact in MSA and is decreased in PD+OH and PAF.

Fourth, one should test for loss of sympathetic noradrenergic nerves. This may be done by cardiac sympathetic neuroimaging, assaying plasma catechols, using

neuropharmacologic probes, or examining skin biopsies for loss of innervation in pilomotor muscles or in blood vessel walls.

MULTIPLE SYSTEM ATROPHY (MSA)

Synopsis:

Mid-aged or elderly of either sex and any race.

Not inherited or infectious.

Chronic, persistent autonomic failure.

Signs of brain disease, such as slurred speech, rigidity, tremor, poor coordination.

Relentless progression over years.

Multiple system atrophy (“MSA”) is a disease that involves progressive degeneration of multiple portions of the central nervous system, including portions that regulate the autonomic nervous system. Several unconscious “vegetative” functions fail, such as digestion, urination, speech and swallowing mechanisms, and cardiovascular reflexes.

No one knows what causes MSA. There is no convincing evidence that in the U.S. the disease is inherited. No environmental toxin is known to cause it. According to one view, MSA results from a form of auto-immune process, where the patient’s immune system attacks and destroys particular brain cells.

Brain tissue from MSA patients shows abnormal accumulations of alpha-synuclein in glial cells (glial cytoplasmic inclusions, or GCIs), which are not neurons. Perhaps the accumulations

interfere with the ability of glial cells to produce nerve growth factors such as glial cell line-derived neurotrophic factor (GDNF). Whether the accumulations cause or are a result of the disease and the mechanisms by which alpha-synuclein accumulates in glial cells are unknown.

MSA has different forms, which result in different symptoms and signs. In the parkinsonian form of MSA (MSA-P) the patient has symptoms and signs of Parkinson's disease, such as stooped posture, muscular rigidity, and slow initiation of movement. Unlike in Parkinson's disease, these problems usually do not respond well to treatment with Sinemet™, the most commonly used drug for Parkinson's disease, and there usually is no "pill roll" resting tremor.

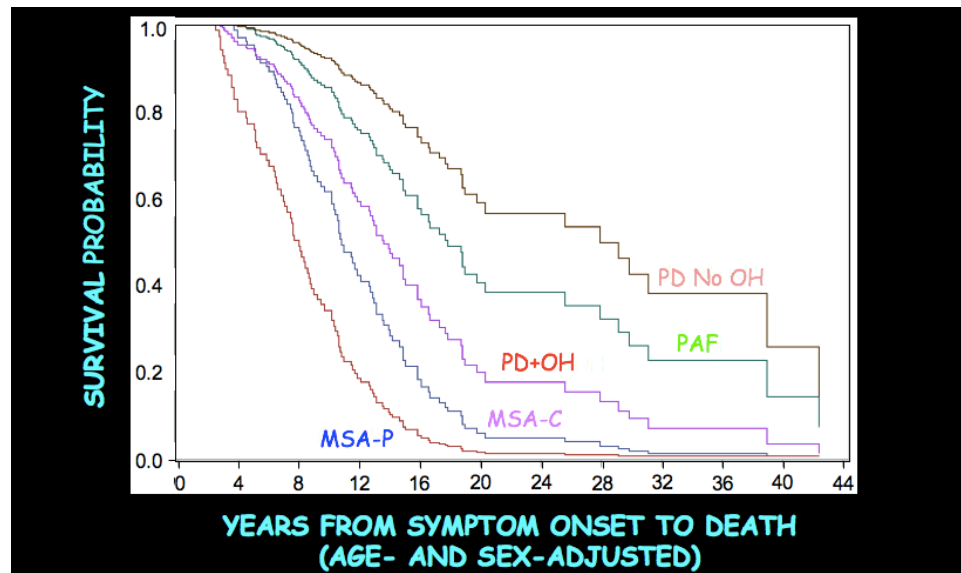
In the cerebellar form of MSA (MSA-C) the patient has symptoms and signs of failure of the cerebellum, which is a part of the brain that plays an important role in coordinated movements, coherent speech, balance, and accurate gait. If the patient has a tremor, it worsens with intentional movements. The typical patient also has slurred speech and a wide-based, "drunken sailor" type gait.

Some patients have both parkinsonism and cerebellar ataxia. There used to be a "mixed" form of MSA, but this classification was abandoned. Now some investigators diagnose MSA-P or MSA-C based on the main symptoms at the time of onset of the movement disorder, and others diagnose MSA-C only if there is cerebellar ataxia and no evidence of parkinsonism at any time in the disease course. By either approach, MSA-C is less common than is MSA-P.

MSA is progressive and eventually lethal. The median survival

from the time of onset of the movement disorder (parkinsonism or cerebellar ataxia) is about a decade.

MSA differs from multiple sclerosis, which is characterized clinically by remissions and exacerbations and by relatively few changes in functions of the autonomic nervous system.



Survival is poor in MSA, whether of the parkinsonian (MSA-P) or cerebellar (MSA-C) types.

MSA always involves one or more symptoms or signs of failure of the autonomic nervous system. Failure of the parasympathetic nervous system produces urinary retention and incontinence, constipation, and erectile failure in men. Failure of the sympathetic noradrenergic system produces a fall in blood pressure when the patient stands up (orthostatic hypotension) or after a meal (post-prandial hypotension), resulting in symptoms such as dizziness, weakness, or faintness upon standing or after eating.

MSA with a fall in blood pressure standing has been called the Shy-Drager syndrome, but this term is no longer used.

Investigators used to equate MSA with the “Shy-Drager syndrome,” which by definition involves orthostatic hypotension (OH). Others considered MSA to be an umbrella diagnosis that includes the Shy-Drager syndrome when OH figures prominently in the clinical presentation but also includes forms where signs of cerebellar atrophy or parkinsonism stand out. The term, Shy-Drager syndrome, is no longer used as a diagnosis.

Symptoms and signs of other brainstem degeneration in MSA include particular abnormalities in eye movements (as in progressive supranuclear palsy), slurred speech, poorly coordinated swallowing, abnormal breathing (e.g., stridor), and repeated aspiration, where swallowed food goes into the airway. These problems occasionally occur in patients with MSA who do not have orthostatic hypotension or other evidence of failure of the sympathetic nervous system.

The parkinsonian form of MSA can be difficult to distinguish clinically from Parkinson’s disease with orthostatic hypotension.

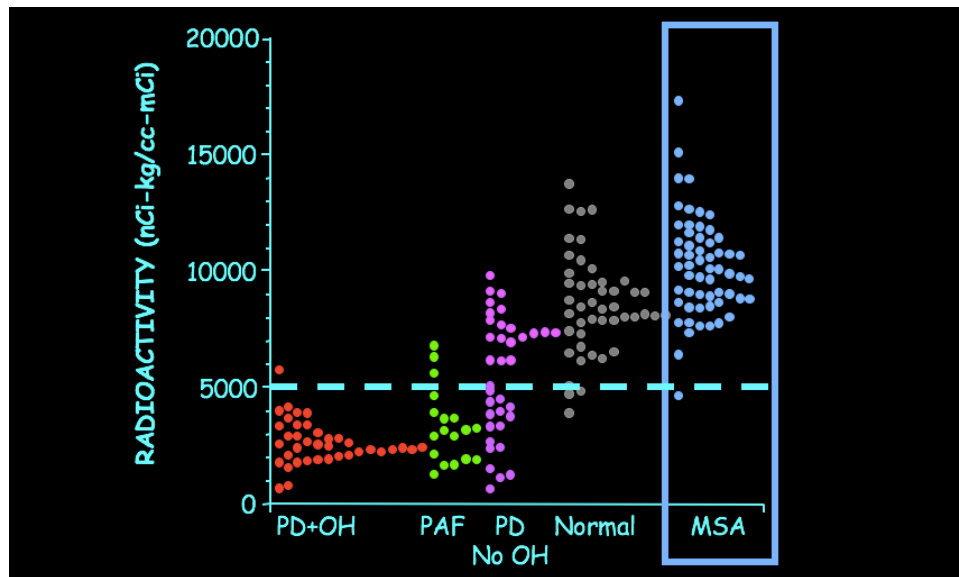
Distinguishing the parkinsonian form of MSA (MSA-P) from Parkinson’s disease with autonomic failure can be a difficult diagnostic challenge. In MSA it is thought that the autonomic failure reflects loss of the ability to regulate sympathetic and parasympathetic nerve traffic in the nerves, but the nerves

themselves are intact. This appears to be a major difference between MSA and Parkinson's disease, in which autonomic failure typically is associated with a loss of nerves of the sympathetic noradrenergic system.

Because of the presence of intact sympathetic nerves, patients with MSA have large increases in blood pressure when they receive drugs such as yohimbine that release norepinephrine from sympathetic nerves and have large decreases in blood pressure when they receive drugs such as trimethaphan that decrease release of norepinephrine from sympathetic nerves. The fact that trimethaphan, which works by blocking transmission of autonomic nerve impulses in the ganglia, decreases blood pressure in patients with MSA means that in MSA the problem is not so much decreased autonomic nerve traffic as failure of the brain to regulate that traffic appropriately.

Patients with MSA appear to have approximately normal nerve traffic in intact sympathetic noradrenergic nerves when they are lying down, and so while they are lying down they usually have normal plasma levels of norepinephrine, the chemical messenger of the sympathetic noradrenergic system. The patients typically have a failure to increase sympathetic nerve traffic when they stand up, and so they have a failure to increase plasma norepinephrine levels normally when they are tilted upright. In contrast, patients with pure autonomic failure, who have a loss of sympathetic nerves, usually have low plasma levels of norepinephrine and of DHPG, the main neuronal metabolite of norepinephrine, even when the patients are lying down.

Another way to distinguish MSA from pure autonomic failure and from Parkinson's disease with orthostatic hypotension (PD+OH) is by cardiac sympathetic neuroimaging. In this type of test, the patient receives an injection of a radioactive drug that gets taken up by sympathetic nerves. The sympathetic nerves in organs such as the heart become radioactive, and the nerves can be visualized by scans that detect where the radioactivity is, in a manner similar to commonly used clinical tests such as bone scans or brain scans.

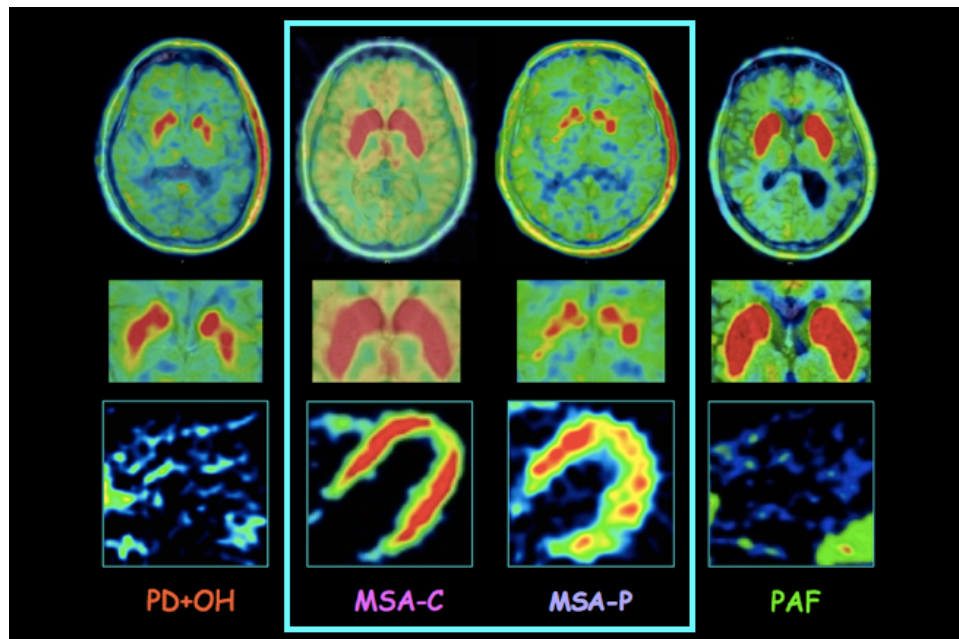


MSA patients usually have neuroimaging evidence for normal cardiac sympathetic innervation. The dashed line shows the lower limit of normal.

Since in MSA the sympathetic nerves are usually present in the organs, scanning after injection of one of these drugs visualizes the sympathetic innervation. In contrast, in pure autonomic failure and in PD+OH, where the sympathetic noradrenergic nerves typically are lost, sympathetic neuroimaging fails to visualize the sympathetic innervation of the heart.

In a patient with parkinsonism and OH, the finding of normal results of cardiac sympathetic neuroimaging excludes PD+OH and supports MSA-P.

In our experience so far, patients with MSA-P always have abnormal putamen ^{18}F -DOPA-derived radioactivity, whereas patients with MSA-C can have normal radioactivity. Cardiac ^{18}F -dopamine-derived radioactivity is normal in most MSA-P patients and (again in our experience) in all MSA-C patients.



The cerebellar and parkinsonian forms of MSA usually involve intact cardiac sympathetic innervation. MSA-P is associated with evidence for loss of putamen dopaminergic innervation.

There is no known treatment that slows the neurodegenerative process in MSA. There are several ways to treat problems as they arise. For orthostatic hypotension the patient should sleep

with the head of the bed elevated on blocks, to minimize orthostatic intolerance after getting out of bed in the morning. The patient should take frequent, small meals and avoid extremes of temperature. Fludrocortisone and a high salt diet may improve orthostatic intolerance, but at the cost of worsening supine hypertension.

Supine hypertension if severe can be alleviated by a calcium channel blocker, an angiotensin II receptor blocker, or nitroglycerine paste or patch. The patient should stay as active physically as possible and have a home exercise program. Physical medicine and rehabilitation efforts have the goal of maximizing mobility and minimizing risk of aspiration.

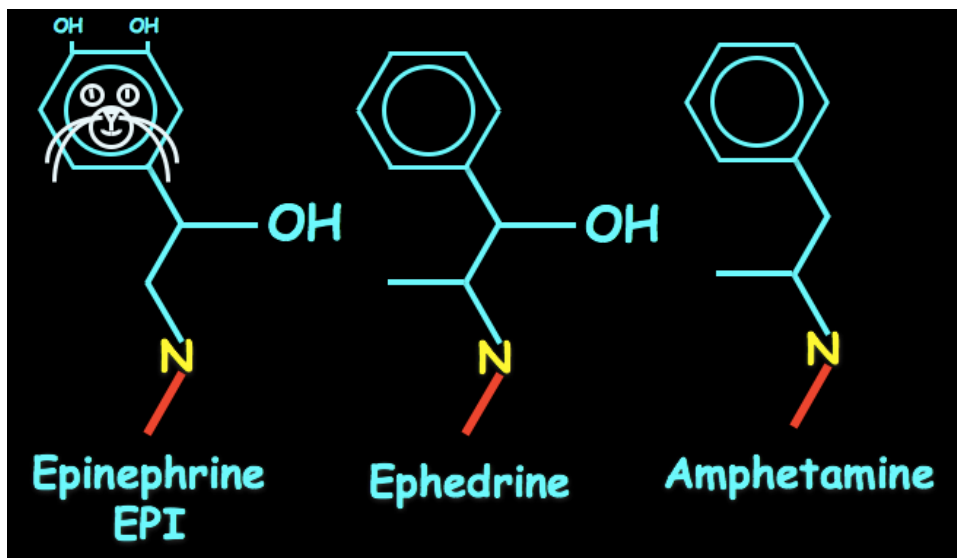
Because of steadily worsening difficulty with coordination of speech and swallowing mechanisms, patients with MSA have a high risk of aspiration (inhalation of a foreign body into the airway), aspiration pneumonia, bloodstream infection, or sudden death from cessation of breathing.

Ma Huang

I once had a patient with multiple system atrophy (MSA) who first came to medical attention because of a hypertensive crisis after taking *ma huang* tea.

Ma huang is a Chinese medicinal herb from the shrub, *Ephedra sinica*. As the name indicates, the active ingredient in *ma huang* is ephedrine. The patient took *ma huang* tea in the hope this would give him more energy and reduce fatigue. Instead, he developed a paroxysmal headache, and in the emergency

room he had extreme hypertension that led to an initial diagnosis of a subarachnoid hemorrhage, which it turned out he did not have.



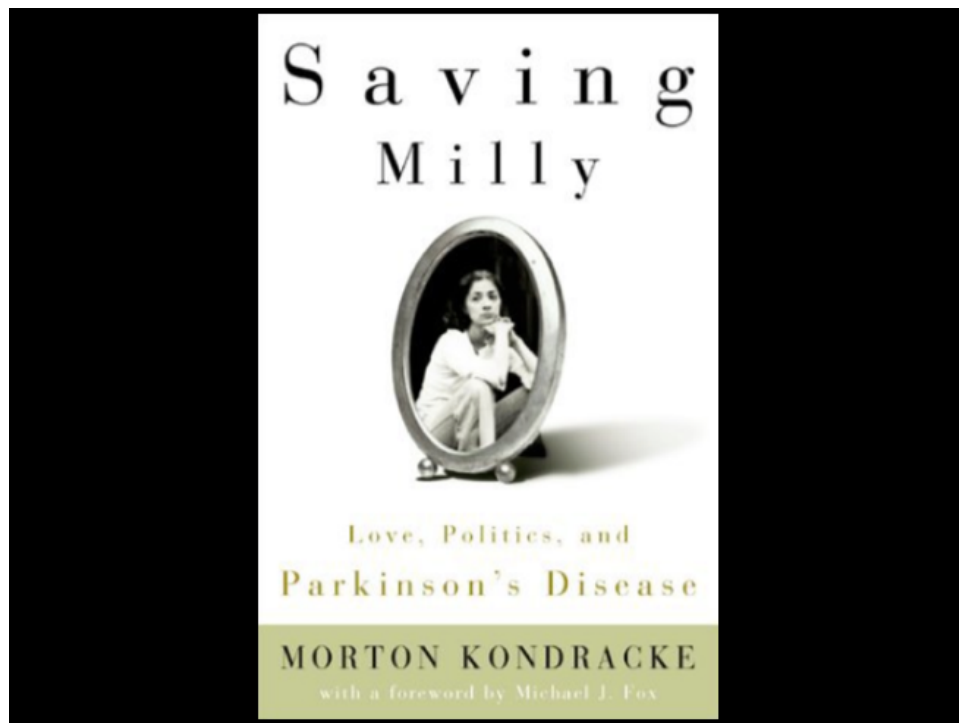
Ephedrine resembles epinephrine and amphetamine.

What he did have was MSA. Patients with MSA have arterial baroreflex failure, resulting in an inability to “buffer” acute changes in blood pressure by compensatory changes in sympathetic noradrenergic system outflows. Ephedrine is a classic sympathomimetic amine that is in the family of amphetamines. Ephedrine augments delivery of norepinephrine to its receptors in the cardiovascular system and therefore increases blood pressure. In the setting of baroreflex failure, ephedrine evokes an exaggerated increase in blood pressure.

Because of morbidity and mortality related to ephedra, the US FDA banned the sale of dietary supplements containing ephedra, including *ma huang* tea, in 2004.

Poster Child for the Wrong Disease?

Millicent (Milly) Kondracke, the wife of the political commentator Morton Kondracke, suffered for many years with a progressive neurodegenerative disease that was called “Parkinson’s-plus,” because her condition included parkinsonism but also some features not typically seen in Parkinson’s disease (PD).



Milly Kondracke was thought to have a variant form of Parkinson's disease.

One of the most prominent was slurred speech. Eventually her speech became so garbled that she had to use an alphabet board (augmentative communication board) or a computer to communicate.

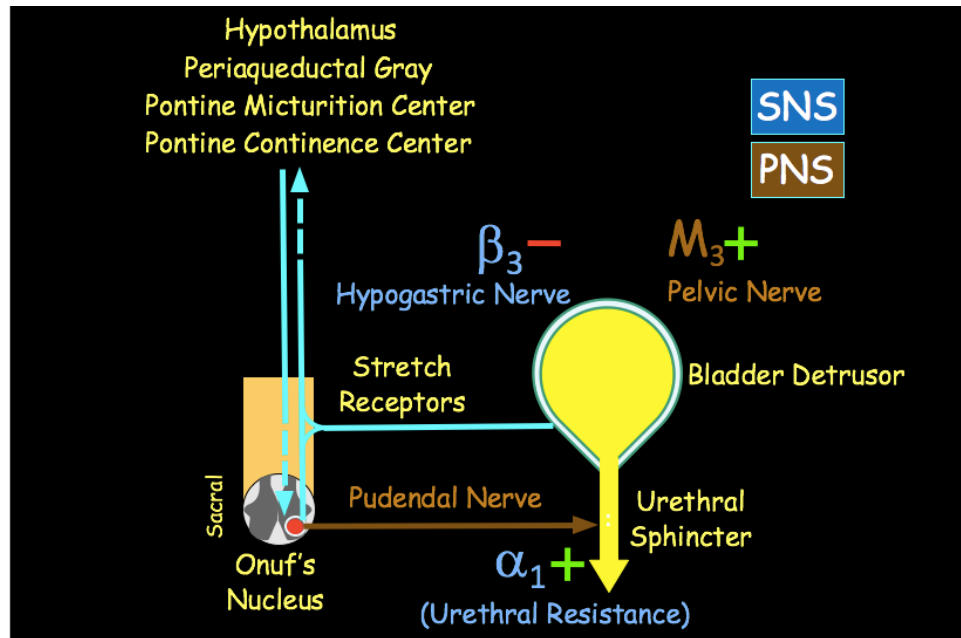
Despite this limitation Milly became famous as a highly effective activist and advocate for increased funding targeting PD. She was gracious but determined, forthright, and courageous. Her husband, Morton, wrote a book about her that became a best-seller and the basis for a made-for-TV movie, “Saving Milly.”

The book mentions that she had been a research participant in one of my studies at the NIH Clinical Center. I suspected she didn’t have PD but had MSA, because of her slurred speech and normal cardiac ^{18}F -dopamine-derived radioactivity. For reasons of confidentiality I can’t state whether I was correct in this suspicion.

Onuf Is Enough

In the evaluation of a patient with possible MSA, the finding of urinary retention is important. Urinary retention is much more common in MSA than in Parkinson’s disease with orthostatic hypotension.

The reason is degeneration in a region called Onuf’s nucleus, which is in the anterior horn of the sacral spinal cord. Onuf’s nucleus receives descending input from the “continence center” in the pons of the brainstem, and it projects to the urethral sphincter by way of the pudendal nerve. Stretch receptors in the bladder wall send afferent information to the spinal cord, and the signal is transmitted both to the brainstem and to Onuf’s nucleus, completing long-distance and local negative feedback loops.



Neuronal degeneration in Onuf's nucleus in MSA manifests with urinary retention and the need to self-catheterize.

PURE AUTONOMIC FAILURE (PAF)

Synopsis:

Mid-aged or elderly of either sex and any race.

Chronic, persistent fall in blood pressure during standing up.

No signs of brain disease.

Not inherited or infectious.

Can go on for many years.

May evolve into Parkinson's disease with orthostatic hypotension or Lewy body dementia.

Pure autonomic failure (PAF, previously called idiopathic orthostatic hypotension and Bradbury-Eggleston syndrome) is the prototype of primary chronic autonomic failure. PAF is a rare disease.

PAF features persistent falls in blood pressure when the patient stands—orthostatic hypotension—in the absence of signs of central nervous system disease and in the absence of other known causes of orthostatic hypotension. The orthostatic hypotension results from sympathetic neurocirculatory failure.

Pure autonomic failure, while chronic and causing disability, is not thought to be lethal.

Patients report progressively worsening dizziness standing up, after a large meal, upon exposure to environmental heat, or after exercise. Because of severe orthostatic hypotension, pure autonomic failure patients often learn to sit or stand with their

legs twisted pretzel-like, since this decreases pooling of blood in the legs.

In men, erectile failure is an early symptom. Often the patients have decreased sweating.

In patients with pure autonomic failure, blood pressure responses to the Valsalva maneuver show the abnormal pattern that indicates sympathetic neurocirculatory failure. The Valsalva maneuver is discussed in the chapter about tests for dysautonomias.

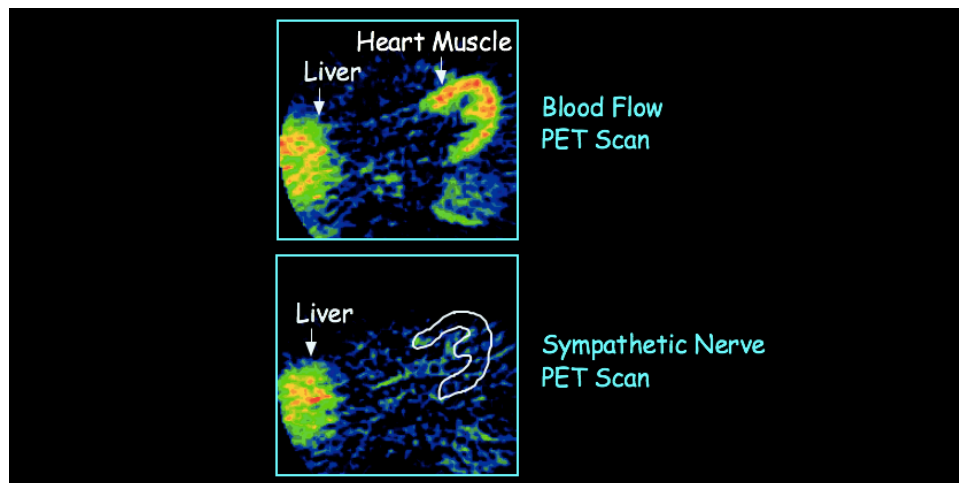
The sympathetic neurocirculatory failure and orthostatic hypotension in pure autonomic failure typically result from loss of sympathetic nerves—in particular, nerves of the sympathetic noradrenergic system.

Drug tests can confirm a diagnosis of pure autonomic failure. Because of the loss of sympathetic nerves, drugs that release norepinephrine from sympathetic nerves, such as yohimbine, tyramine, amphetamine, and ephedrine, produce relatively small increases in the blood pressure. In contrast, drugs that directly stimulate norepinephrine receptors, such as midodrine, phenylephrine (Neo-Synephrine™), and droxidopa (Northera™), constrict blood vessels and increase the blood pressure.

Because of the phenomenon of “denervation supersensitivity,” in which receptors for norepinephrine increase and other adaptive processes probably occur that exaggerate constriction of blood vessels, patients with pure autonomic failure can have

surprisingly large increases in blood pressure in response to the receptor-stimulating drugs.

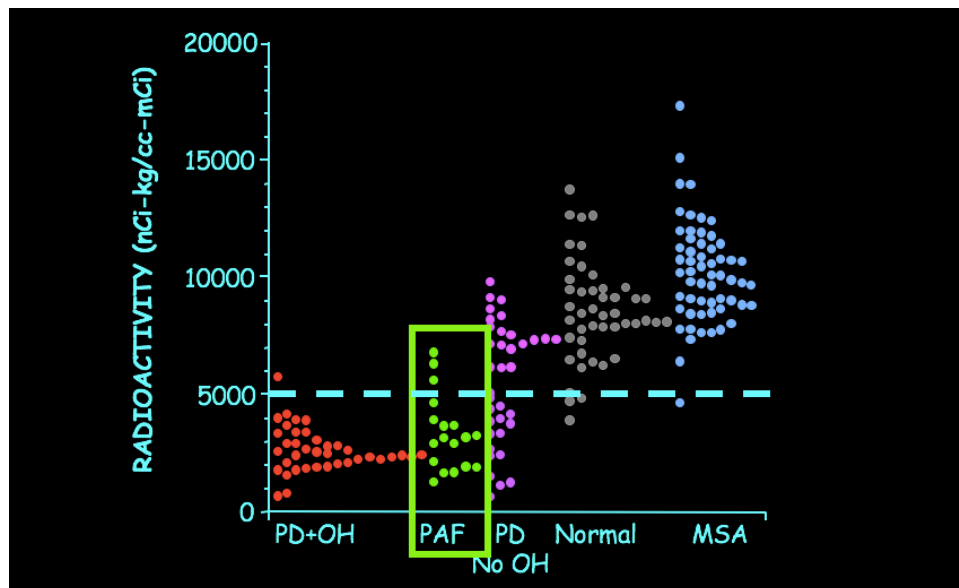
As a result of loss of sympathetic nerves, plasma norepinephrine levels typically are low in PAF, even with the patient lying down, and because of concurrent baroreflex-sympathoneural failure the levels fail to increase when the patient stands. PAF patients usually have low plasma levels of dihydroxyphenylglycol (DHPG), which is a measure of the amount of norepinephrine-containing nerves.



Sympathetic neuroimaging tests such as fluorodopamine PET scanning of the chest often produce remarkably graphic results in PAF, with a failure to visualize the heart muscle at all.

Another way to identify PAF is from sympathetic neuroimaging. In this type of test, the patient receives an injection of a radioactive drug that is taken up by sympathetic nerves. The sympathetic nerves in organs such as the heart become radioactive, and the nerves can be visualized by scans that detect where the radioactivity is, in a manner similar to commonly used clinical tests such as bone scans or brain scans.

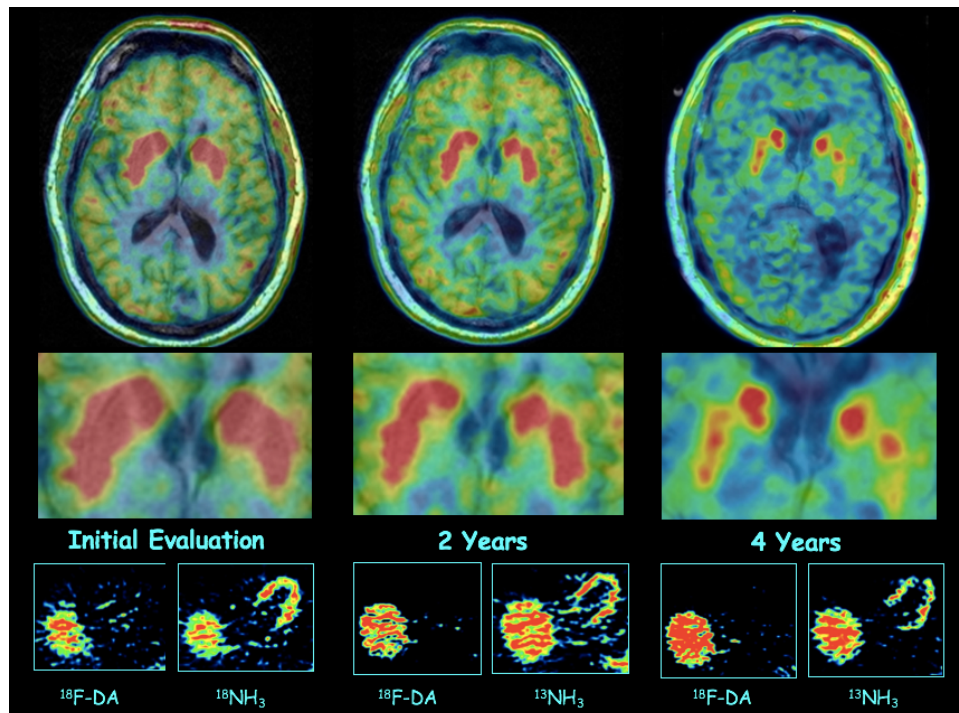
Since in PAF the sympathetic nerves usually are absent in the organs, scanning after injection of one of these drugs fails to visualize the sympathetic innervation.



Most patients with PAF have evidence of cardiac sympathetic denervation by ^{18}F -dopamine PET scanning. The dashed line indicates the lower limit of normal.

No one knows what causes PAF. It is not inherited, and no known environmental toxin causes it. Studies of tissues from patients with PAF indicate that it is related to Parkinson's disease, even though the patients do not have evidence of parkinsonism or other brain disease.

Pure autonomic failure can sometimes be difficult to distinguish from early Parkinson's disease with orthostatic hypotension (PD+OH). At least in some patients, PAF evolves into dementia with Lewy bodies and (PD+OH), but the frequency of this happening is a topic of current research.



Evolution of PAF into dementia with Lewy bodies and Parkinson's disease with orthostatic hypotension. Striatal ^{18}F -DOPA-derived radioactivity is normal at first but then takes on the abnormal appearance typically found in PD.

Rarely, patients who have the symptoms, signs, and clinical laboratory abnormalities that characterize PAF have evidence for normal sympathetic innervation of the heart. This can be a clue that the patient has autonomic failure not because of a loss of sympathetic nerves but from interference with transmission of the control signals to those nerves in the ganglia. Such patients can have an antibody to the nicotinic receptor, a condition that has been called autoimmune autonomic ganglionopathy (AAG), which is presented separately.

Treatment of PAF is directed mainly at the orthostatic hypotension, which virtually always is severe and disabling.

Clinicians usually recommend elevation of the head of the bed. Body stockings may or may not help. The patient should not take large meals, because this may cause the blood pressure to decrease (post-prandial hypotension).

Drugs that release norepinephrine from sympathetic nerves, such as ephedrine, Ritalin™, or yohimbine, may not work well, because of the lack of nerves, whereas drugs that artificially stimulate receptors for norepinephrine, such as midodrine and droxidopa, can be very effective. Fludrocortisone, a high salt diet, and potassium supplementation are also commonly used.

Death in a Jet's Bathroom

A patient with pure autonomic failure (PAF) was flying internationally and went to the bathroom in the jet during flight. When he didn't come out, eventually the staff broke open the door and found him dead.

One may speculate about what went wrong in these patients. Patients with neurogenic orthostatic hypotension have an inability to tighten blood vessels reflexively to counter effects on blood pressure of decreased venous return to the heart. That is, when the venous return to the heart decreases, the blood pressure decreases. When a person strains at stool, the high pressure in the abdomen decreases venous return to the heart, and this exacerbates the fall in blood pressure. Eventually there may be a severe enough fall in blood pressure that the patient loses consciousness and falls limp to the floor. But in a jet's bathroom the patient would not be able to do this. If the patient were kept sitting, the blood flow to the brain would become

dangerously low.

I had another PAF patient who was celebrating his birthday with his family at a local restaurant when he excused himself to go the bathroom. He didn't return, and he was found in cardiac arrest in the bathroom. Although he was resuscitated successfully by injection of adrenaline for asystole, he died a few days later. The patient had noted angina-like chest pressure, but autopsy showed no important coronary artery disease.

It seems reasonable to speculate that in PAF, severe orthostatic hypotension combined with straining in the bathroom can produce critical decreases in cerebral and coronary blood flows.

A Dive into a Nightstand

Dream enactment behavior occurs commonly in autonomic synucleinopathies. The patient acts out his or her dreams and thrashes about in bed. Polysomnography shows an absence of the normal loss of limb muscle tone during rapid eye movement (REM) sleep, and the condition is called REM Behavior Disorder, or RBD.

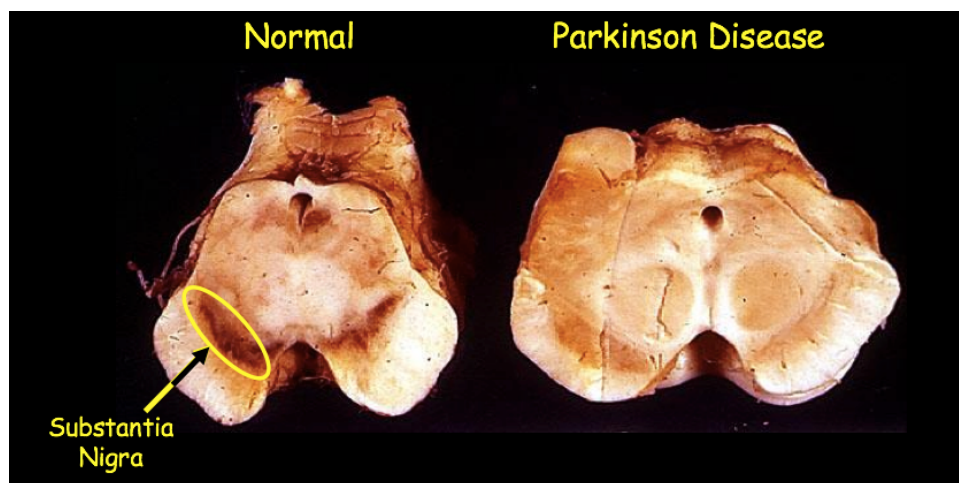
In men with RBD the dream often involves an attempt at active defense. Men with RBD can attack their bed partners and cause substantial physical—and psychological—trauma, all while asleep.

At the NIH Clinical Center, we had a patient with PAF who reported he had had dream enactment behavior for many years.

He had been a troop leader in Vietnam. In his dream he would be with his soldiers on a paved road, when an enemy plane would fly toward them, strafing the road. He would yell to dive to the side of the road. One night in the NIH Clinical Center he dove headfirst into his bedstand. He lacerated his head, but luckily there was no evidence of brain damage from the fall.

PARKINSON'S DISEASE (PD)

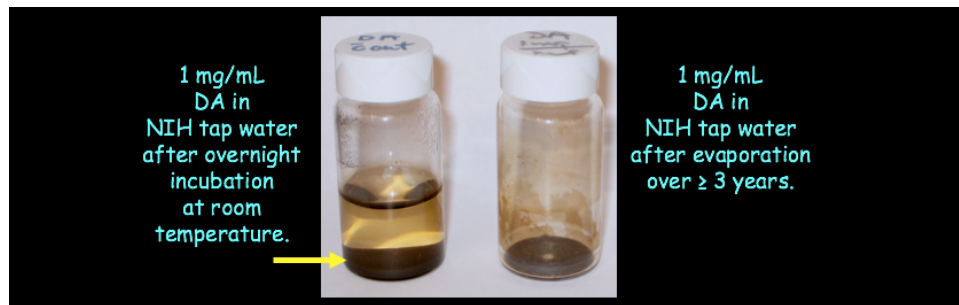
Parkinson's disease (or Parkinson disease, PD) is the second most common neurodegenerative disease of the elderly (the first is Alzheimer's disease). PD is well known to be characterized by a movement disorder that includes slowness (bradykinesia), limb rigidity, tremor at rest, and imbalance.



Loss of pigmentation in the substantia nigra is a classic neuropathologic finding in Parkinson's disease.

The key pathologic change in the brain that is seen in PD is the loss of black pigmentation in the substantia nigra (from the Latin for “black substance”) in the midbrain of the brainstem.

The loss of black pigment probably reflects a decreased number of neurons that contain the catecholamine, dopamine. It is no coincidence that dopamine in solution spontaneously oxidizes and polymerizes to form a black pigment—melanin (from the Greek for “black”).

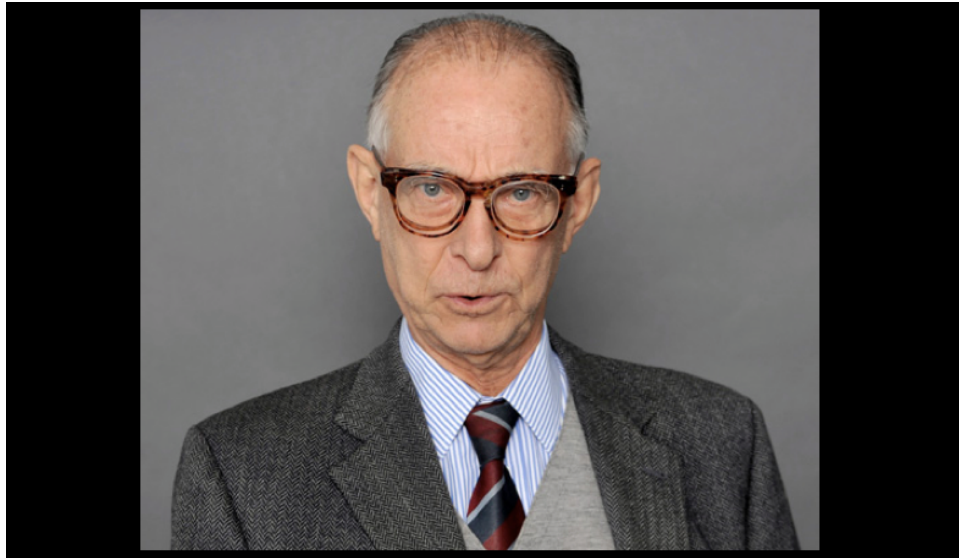


Dopamine in solution spontaneously oxidizes and polymerizes to form a black pigment, melanin.

Nerve fibers from the substantia nigra travel to the striatum (plural striata), a pair of large structures on each side of the brain further up in the central nervous system. The striatum has two parts—the caudate nucleus and the putamen. The putamen is the main damaged site in PD.

Profound depletion of DA in the striatum is the classic neurochemical abnormality in PD. This was first described by Oleh Hornykiewicz in 1960. The most severe DA depletion is in the putamen. All current approved treatments of PD work directly or indirectly by countering effects of striatal DA depletion. While often effective in alleviating motor symptoms, no treatment has been proven to slow the loss of nigrostriatal neurons.

PD was the first neurodegenerative disease for which the underlying neurochemical abnormality was identified—severe depletion of the catecholamine dopamine (DA).



Oleh Hornykiewicz, discoverer of the striatal dopamine depletion that causes the movement disorder in PD.

Alleviation of dopamine deficiency in PD by levodopa treatment—introduced by Hornykiewicz—was revolutionary in the history of medical neuroscience.

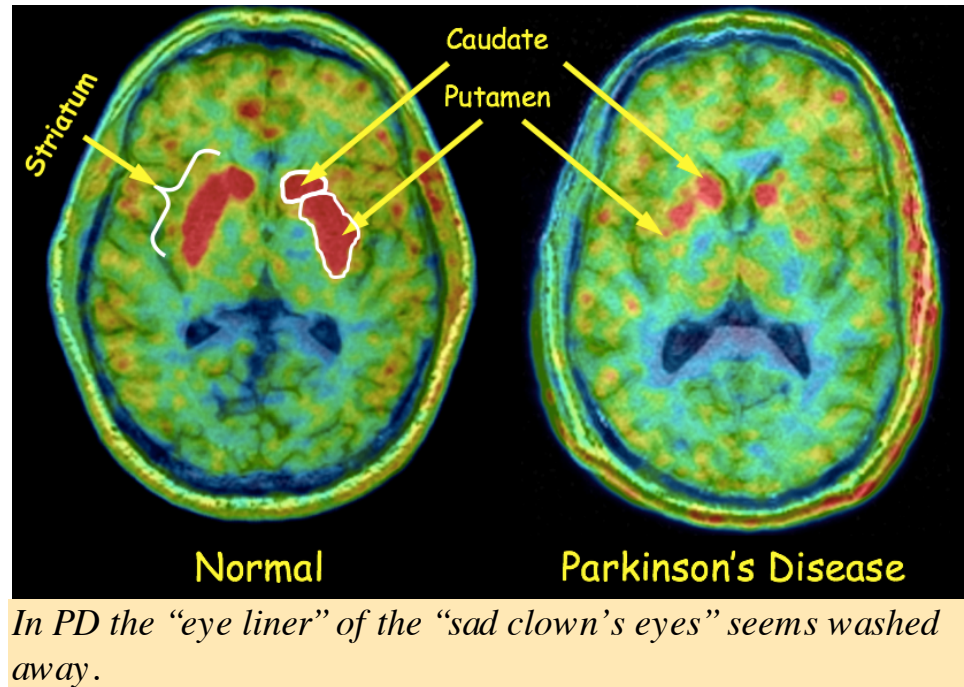
The Sad Clown's Eyes

^{18}F -DOPA PET scanning is an excellent way to see if there is a loss of striatal dopamine terminals. On a ^{18}F -DOPA scan, the striata look like a sad clown's eyes.

A special type of brain scan can show the abnormality that causes the movement disorder in PD.

The beady eyes themselves correspond to the head of the

caudate on each side. The eye liner corresponds to the putamen. The putamen is the main site of damage in PD. In PD the eye liner seems washed away. Usually the loss is worse on one side, the side opposite to the side of the movement disorder.

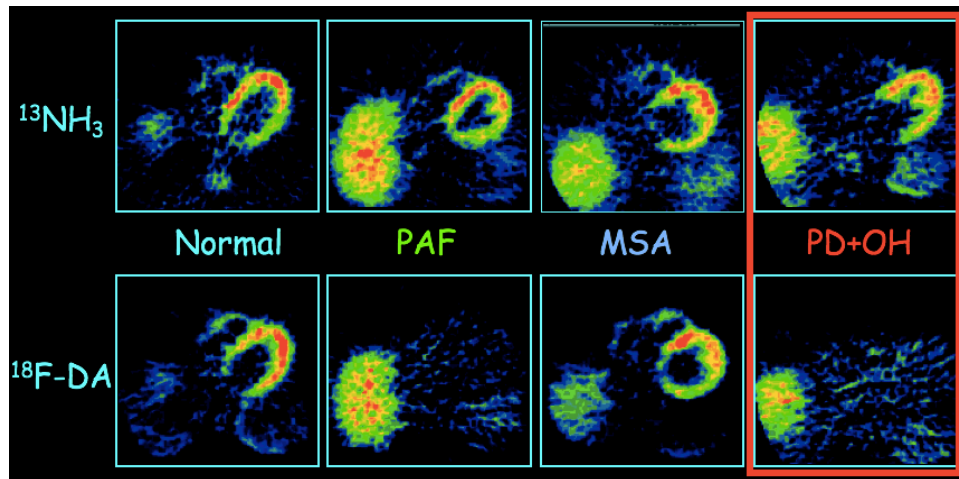


Cardiac Sympathetic Denervation in PD

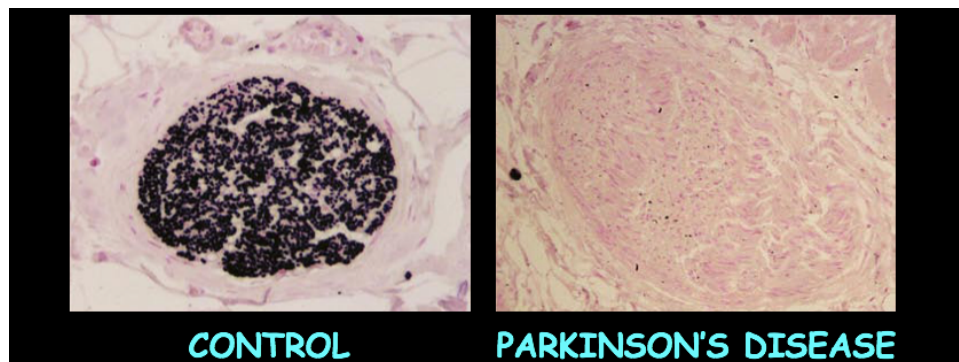
Perhaps surprisingly, most patients with Parkinson's disease have evidence for at least some loss of sympathetic nerves in the heart.

The discovery of loss of cardiac sympathetic nerves in PD provided clear evidence that PD is more than a brain disease and more than a movement disorder. It is also a disease that involves the sympathetic noradrenergic system and involves a

form of dysautonomia. Sympathetic noradrenergic denervation was the first identified mechanism for a non-motor aspect of PD.



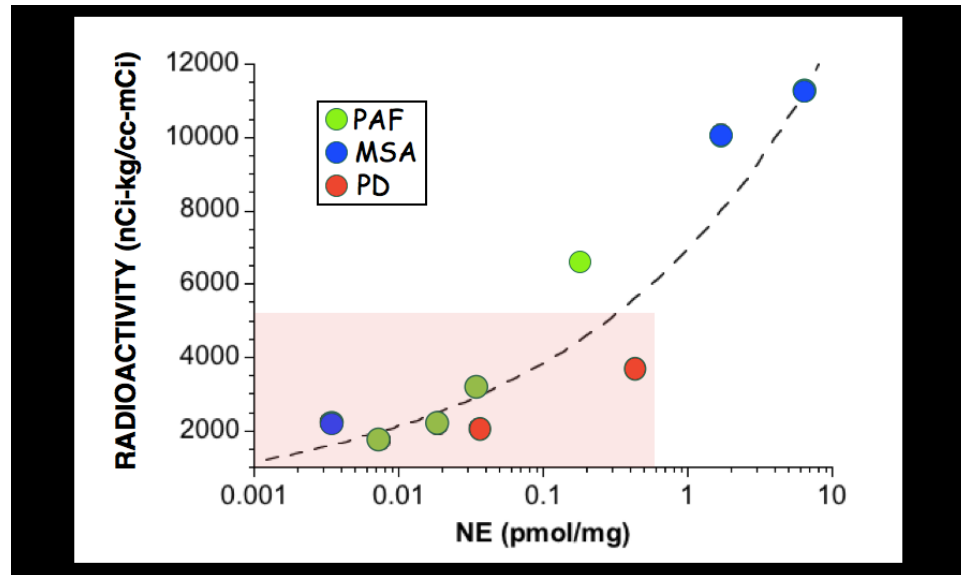
Cardiac sympathetic neuroimaging provided the first evidence for a specific mechanism of a non-motor aspect of PD— loss of noradrenergic nerve terminals.



Markedly decreased immunoreactive tyrosine hydroxylase in epicardial nerve tissue provides pathological confirmation of cardiac sympathetic denervation in PD.

The amount of immunoreactive tyrosine hydroxylase (THir) in epicardial nerve tissue provides a means to examine post-ganglionic sympathetic noradrenergic innervation of the heart.

Epicardial THir is profoundly decreased in PD.



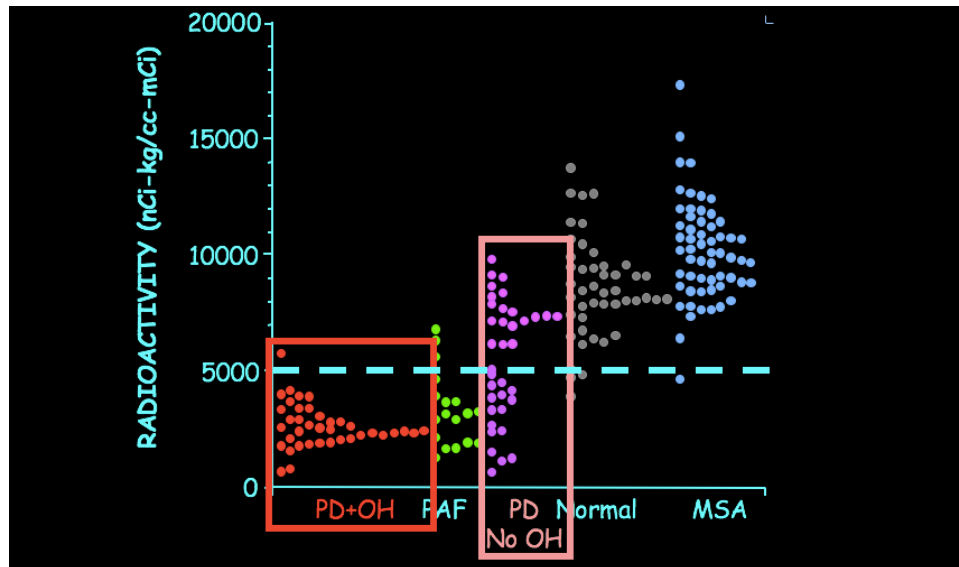
Low ^{18}F -dopamine-derived radioactivity is associated with low norepinephrine in myocardial tissue (pink rectangle).

Across patients with different chronic autonomic failure syndromes, low myocardial ^{18}F -dopamine-derived radioactivity during life is associated with low norepinephrine content in myocardial tissue obtained post-mortem.

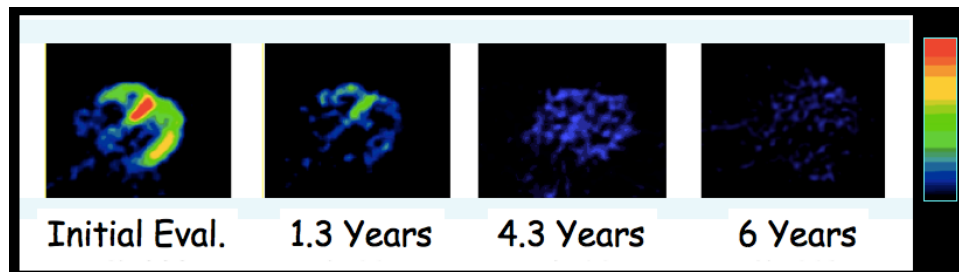
Among PD patients who do not have orthostatic hypotension (PD No OH), about 1/2 have loss of sympathetic nerves throughout the left ventricular myocardium, a substantial minority have partial loss of sympathetic nerves, and a few have normal innervation. The partial loss is in the apex or free wall of the heart. The likelihood of denervation seems greater in PD patients who first notice motor symptoms at a relatively old age.

In PD patients who have a partial loss of the sympathetic nerves

in the heart, when the patients are followed over years, the loss of sympathetic nerves in the heart progresses.



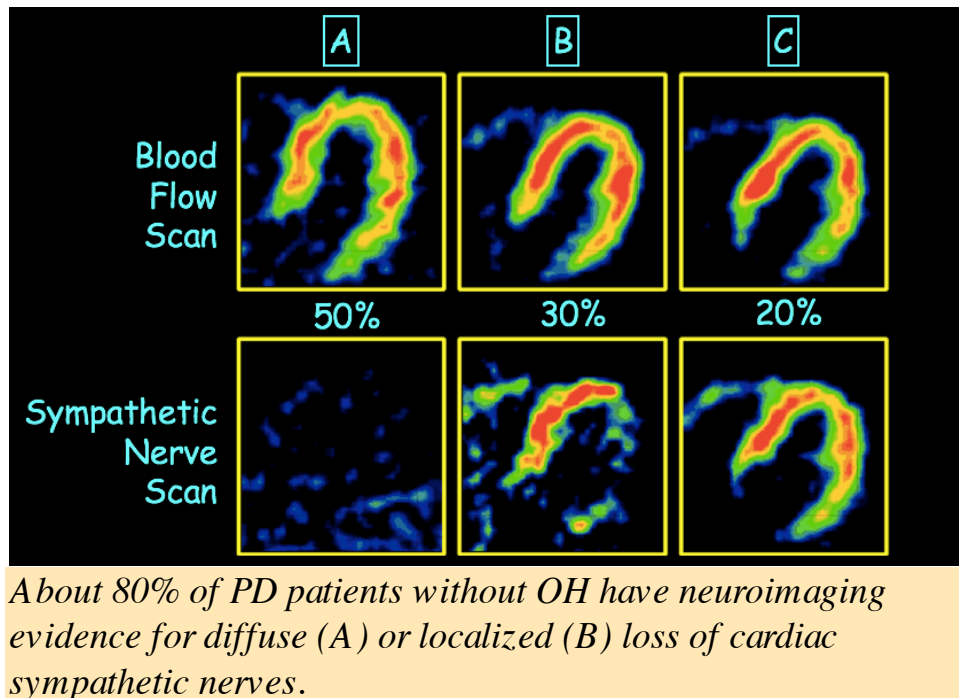
About ½ of PD patients without orthostatic hypotension (PD No OH) and all PD patients with OH have neuroimaging evidence for loss of cardiac sympathetic noradrenergic nerves.



This PD patient had partial cardiac denervation when first seen. The denervation progressed rapidly.

It seems that all PD patients eventually lose cardiac sympathetic nerves. It may take several years for this to begin, but once it does, the loss progresses rapidly.

The functional significance of loss of sympathetic nerves in the heart in Parkinson's disease remains unknown. One would guess that this might cause or contribute to fatigue or to shortness of breath during exercise.



PD with Orthostatic Hypotension (PD+OH)

Synopsis:

Elderly of either sex and any race (usually light skin)
Signs of Parkinson's disease, such as slow movements, rigidity, tremor.
Movement problem improves with Sinemet™ (DOPA+carbidopa).
Chronic, persistent fall in blood pressure standing.
OH can come on before movement problems.

Can be inherited.
Slow progression over years.

Symptoms or signs of autonomic dysfunction occur extremely commonly in PD. These include constipation, urinary frequency and urgency, drooling, erectile failure in men, altered sweating, and orthostatic intolerance due to orthostatic hypotension.

It has been estimated that 90% of PD patients have abnormal autonomic functions.

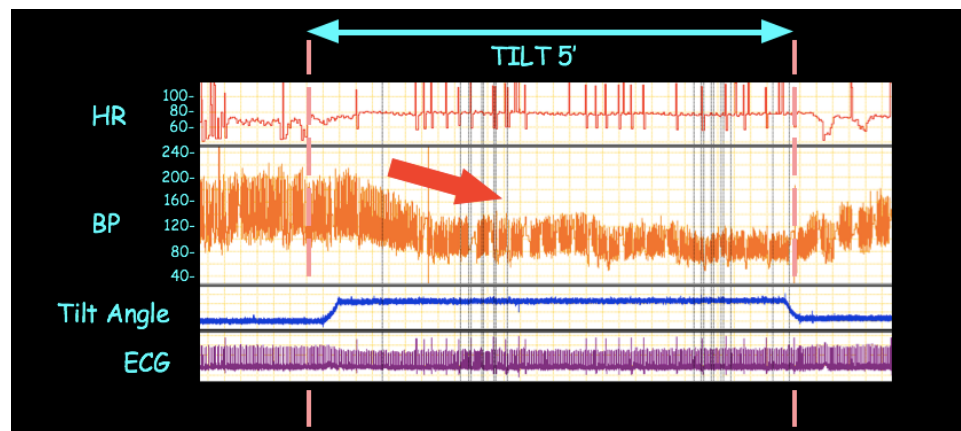
Exactly how these problems, which reflect involvement of different components of the autonomic nervous system, relate to each other is unclear. For instance, the prevalence of constipation and urinary frequency and urgency is about the same regardless of the occurrence of orthostatic hypotension.

Orthostatic hypotension (OH), a fall in blood pressure when the patient stands up, occurs in 30-40% of patients with Parkinson's disease. The frequency of OH is underestimated when clinicians depend on symptoms or signs, because many patients with OH feel nothing wrong when they are upright or have symptoms that are non-specific. The only way to determine accurately whether a patient with PD has OH is to measure the blood pressure after the patient has been lying down for several minutes and then again after the patient has been upright.

Most (but not all) MSA-P patients have neuroimaging evidence

for normal cardiac sympathetic innervation. In the differential diagnosis of PD+OH vs. MSA-P, the finding of normal cardiac sympathetic neuroimaging excludes PD+OH.

Patients with Parkinson's disease and a fall in blood pressure when they stand up have a form of dysautonomia.

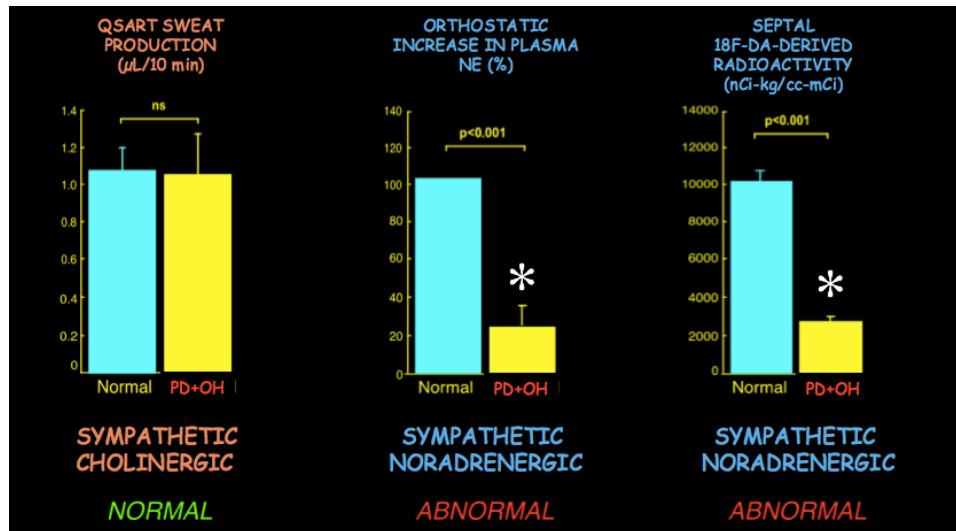


Orthostatic hypotension during head-up tilt table testing in a patient with PD+OH

In contrast, sweat production, which is mainly a function of the sympathetic cholinergic system, can be normal in PD+OH, and the majority of PD+OH patients have normal QSART results.

Patients with Parkinson's disease often have constipation and urinary urgency, frequency, and incontinence. These might reflect a form of failure of the parasympathetic nervous system; however, whether this is the case remains unknown. Decreased traffic in the vagus nerve, the nerve of the parasympathetic nervous system that supplies the heart, appears to cause the constant pulse rate seen in most patients with PD+OH. This

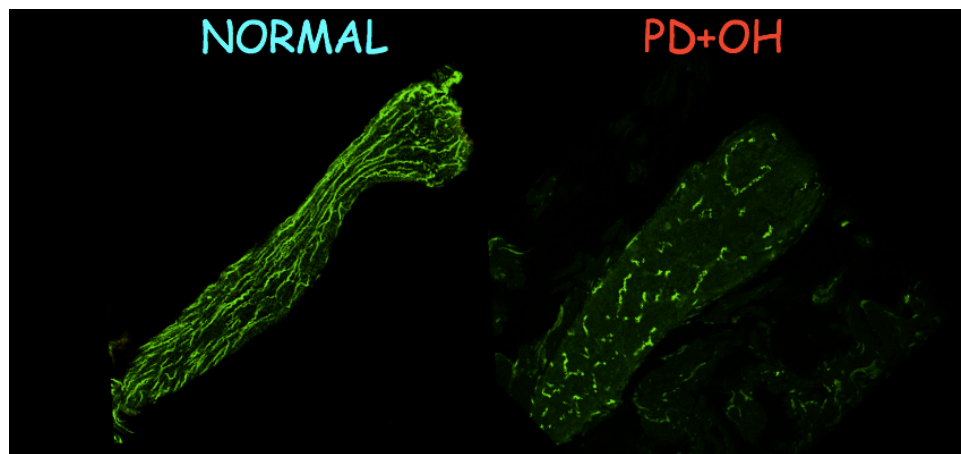
could reflect a loss of parasympathetic nerves or a problem in reflexive regulation of traffic in intact nerves.



In PD+OH, sympathetic cholinergic function is usually normal, whereas sympathetic noradrenergic function (measured by the percent increase in plasma norepinephrine (NE) during head-up tilt table testing or by cardiac sympathetic neuroimaging) is abnormal.

All patients with PD and orthostatic hypotension have a loss of sympathetic nerves in the heart.

Another way to visualize decreased sympathetic noradrenergic innervation in PD+OH is by analyzing skin biopsy tissue. Each hair follicle has a muscle, called *arrector pili* or pilomotor muscle, which is responsible for the hair bristling such as during cold exposure. The *arrector pili* muscles receive mainly sympathetic noradrenergic innervation. The finding of decreased nerve fibers in *arrector pili* muscle fits with loss of sympathetic noradrenergic innervation.



Skin biopsy showing normal sympathetic noradrenergic innervation of arrector pili muscle (left) and markedly decreased, fragmented innervation in a patient with PD+OH (Images courtesy of R. Freeman, C. Gibbons, and N. Wang).

The long-term outlook in PD+OH is worse than in PD without OH (PD No OH). When the movement disorder first becomes apparent, PD+OH patients are on average about a decade older than PD No OH patients; however, PD+OH patients have shorter survival than do PD No OH patients even after adjustment for age.

Non-drug treatments for PD+OH include taking frequent small meals, avoiding prolonged heat exposure, and elevation of the head of the bed on blocks at night.

Drug treatments used for PD+OH include fludrocortisone (with a high salt diet), midodrine, and the recently approved NE precursor L-dihydroxyphenylserine (droxidopa, L-DOPS, Northera™).

Midodrine and droxidopa may be particularly effective drugs to

treat symptomatic OH in PD+OH, because of denervation supersensitivity and baroreflex failure in PD+OH.

In PD+OH patients, symptomatic OH is usually worst in the morning, and the blood pressure creeps up as the day goes on. I usually give 2/3 of the daily dose of midodrine in the early morning, and 1/3 at lunchtime (to avoid post-prandial hypotension). I'm concerned that giving midodrine around the clock may bombard the alpha-adrenoceptors, so that they are no longer supersensitive because of the lack of norepinephrine delivery.

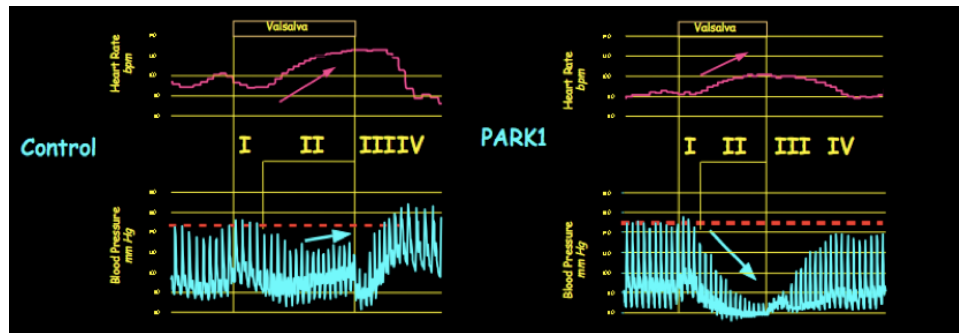
Theoretically, the carbidopa in Sinemet™ used to treat PD would inhibit conversion of L-DOPS to NE, but practically the carbidopa dose required to produce this effect is far more than is found in Sinemet™. Treatments that depend on release of norepinephrine (NE) from sympathetic nerves, such as ephedrine, d-amphetamine, methylphenidate, and yohimbine, may not work well in PD+OH, because of the loss of the noradrenergic nerves, but they may still have effects due to denervation supersensitivity and baroreflex failure augmenting the increases in blood pressure for a given amount of NE release.

The Contursi and Iowa Kindreds

In 1997 the first clear evidence for a genetic cause of PD was reported—mutation of the gene encoding the protein, alpha-synuclein. In large Greek-Italian-American kindred called the Contursi kindred, PD is transmitted as an autosomal dominant trait (half the family members developing PD). A53T mutation

of the alpha-synuclein gene was found to be causative in this family. This rare form of familial PD is called PARK1. Exactly why and how this “typo in the genetic encyclopedia” results in loss of nigrostriatal dopamine neurons remain unsettled.

We had the opportunity to carry out autonomic function testing in a PARK1 patient. He had clear evidence of orthostatic hypotension. Until the evaluation he had never had his blood pressure measured while lying down and then while upright.

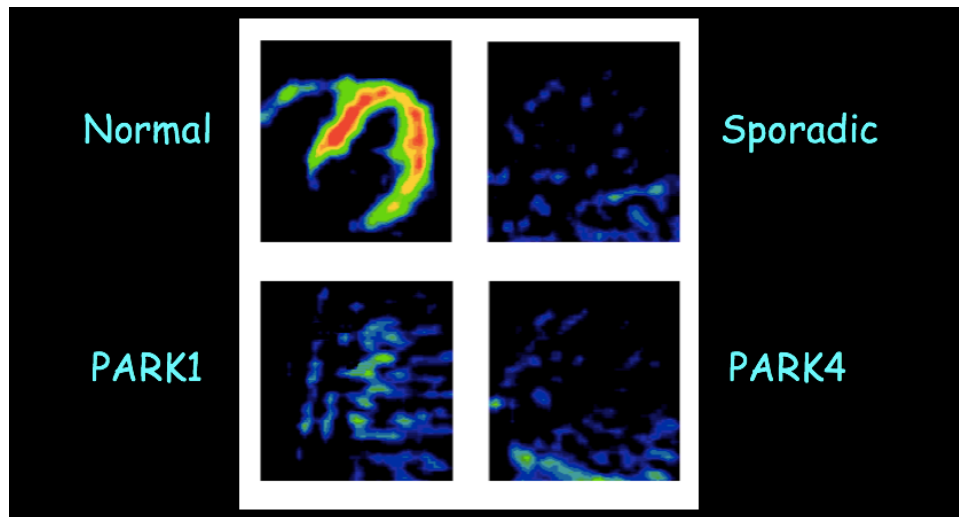


Abnormal pattern of beat-to-beat blood pressure in a patient with familial PD from mutation of the gene encoding alpha-synuclein.

His pattern of beat-to-beat blood pressure associated with performance of the Valsalva indicated sympathetic neurocirculatory failure. During Phase II the blood pressure declined progressively, and in Phase IV there was no pressure overshoot. Since his heart rate increase was blunted for the amount of fall in blood pressure during Phase II, he also had baroreflex-cardiovagal failure.

Cardiac sympathetic neuroimaging in this patient showed markedly decreased ^{18}F -dopamine-derived radioactivity

throughout the left ventricular myocardium, indicating that his neurogenic orthostatic hypotension was the result of both baroreflex failure and loss of sympathetic noradrenergic neurons.



The finding of cardiac sympathetic denervation in PARK1 and PARK4, as in sporadic PD, demonstrates that alpha-synucleinopathy can cause loss of sympathetic noradrenergic neurons.

Another form of familial PD was reported in a kindred called the Iowa kindred. Here the causative abnormality is triplication of the normal alpha-synuclein gene. This form of dominantly inherited PD is called PARK4.

PARK4 patients also have physiological evidence of baroreflex-sympathoneural failure and neuroimaging evidence of cardiac sympathetic denervation.

The findings in PARK1 and PARK4 helped establish that alpha-synucleinopathy can cause not only loss of striatal

dopaminergic innervation but can also cause loss of cardiac sympathetic noradrenergic nerves, neurogenic orthostatic hypotension, and baroreflex failure.

The Fainting Attorney General

In March of 1995, Janet Reno, then 57 years old and two years into her term as the first female US Attorney General, began to notice a tremor in her left hand during her walks around the Capitol in the early morning hours. She was diagnosed with PD.



Janet Reno, 78th Attorney General of the United States

About two years after the motor onset of PD, she fainted in a hot, crowded room during an international conference at the El Camino Real Hotel in Mexico City. The fainting was attributed to gallstones and fatigue. Her doctor, the director of the Parkinson's Disease and Movement Disorder Clinic at the University of Miami, gave the opinion that fainting is not usually associated with PD.

In 1998 she fainted at about 8:30 AM at Full Gospel AME Church in suburban Clinton, MD, also on a hot day. A medical spokesman at the Georgetown University Medical Center stated, “This is just a fainting spell. Her condition is good.”

In 2002, at 63 years old, she fainted again while giving a talk at the University of Rochester during her primary campaign for Governor of Florida. An examining physician stated, “We discovered no link between the incident and her previously reported Parkinson's disease.”

I’m not so sure about the claimed lack of a link between fainting and PD, because of the possibility of PD+OH.

In a patient with chronic autonomic failure, attending a church service on a hot Sunday morning could be a real autonomic stress test, with fainting evoked by severely decreased blood pressure.

First, the patient would likely be standing still for prolonged periods, resulting in blood pooling in the abdomen, pelvis, and legs. Second, in autonomic failure syndromes, orthostatic hypotension is usually worst in the morning. Third, singing increases the pressure in the chest and abdomen and decreases venous return to the heart. Fourth, exposure to environmental heat relaxes blood vessels. Fifth, if a church breakfast preceded the service, blood could have been shunted toward the gut after the meal (post-prandial hypotension). Sixth, if the worshipper felt distressed during the service, high circulating adrenaline levels would relax blood vessels in the skeletal muscle, decreasing total peripheral resistance to blood flow.

Janet Reno died of her disease on November 7, 2016, at the age

of 78.

In PD When does Autonomic Failure Occur?

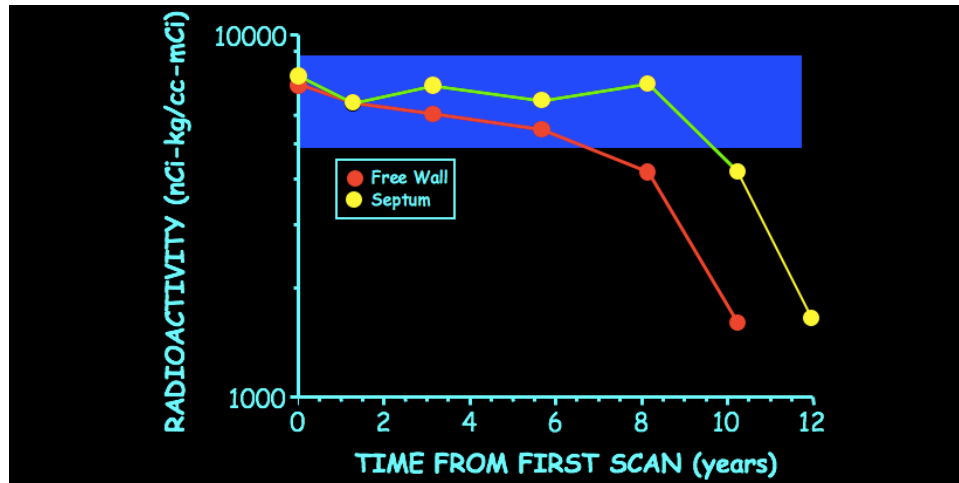
About 90% of PD patients have symptoms or signs of some form of autonomic failure, and about 30-40% have neurogenic orthostatic hypotension. The findings in an important case we reported several years ago demonstrate that cardiac sympathetic denervation can precede the movement disorder by several years. This case is discussed in more detail later in this section.

On the other hand, patients who already have symptomatic PD can have normal or only localized loss of cardiac sympathetic innervation. For instance, several years ago we evaluated a PD patient who did not have orthostatic hypotension and found that she had decreased ^{18}F -dopamine-derived radioactivity in the left ventricular free wall and apex of the heart, but there was normal radioactivity in the septum. Over the course of just a few years the loss of innervation progressed to completion.

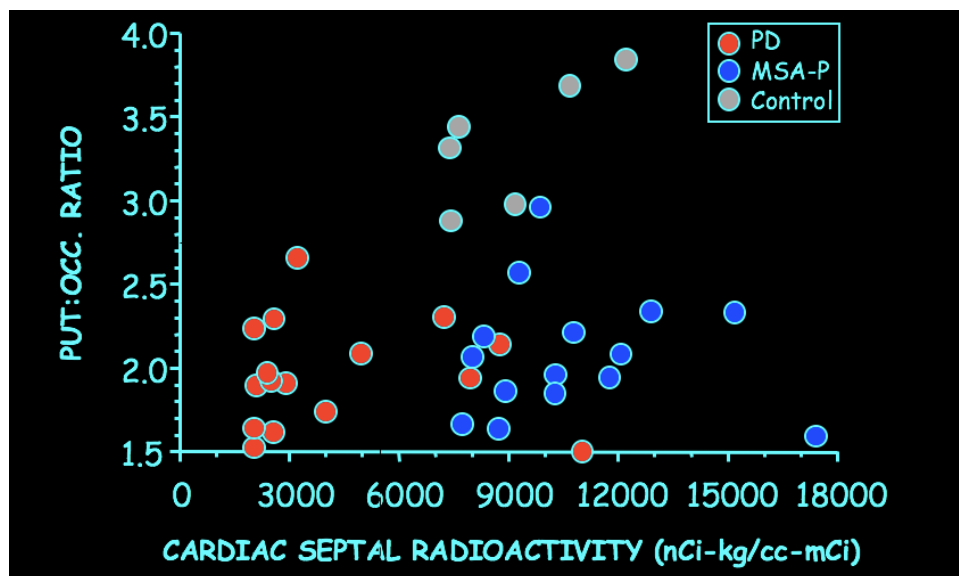
In another patient, who already had PD, cardiac sympathetic innervation seemed normal over about 8 years of follow-up. Then the patient had partial denervation in the free wall. This was followed soon after by diffuse denervation, with loss of innervation in the inter-ventricular septum.

Across synucleinopathies, there is no relationship between the extent of the putamen dopaminergic lesion, as indicated by the putamen:occipital cortex ratio of ^{18}F -DOPA-derived radioactivity, and the extent of the sympathetic noradrenergic lesion, as indicated by septal myocardial concentration of ^{18}F -

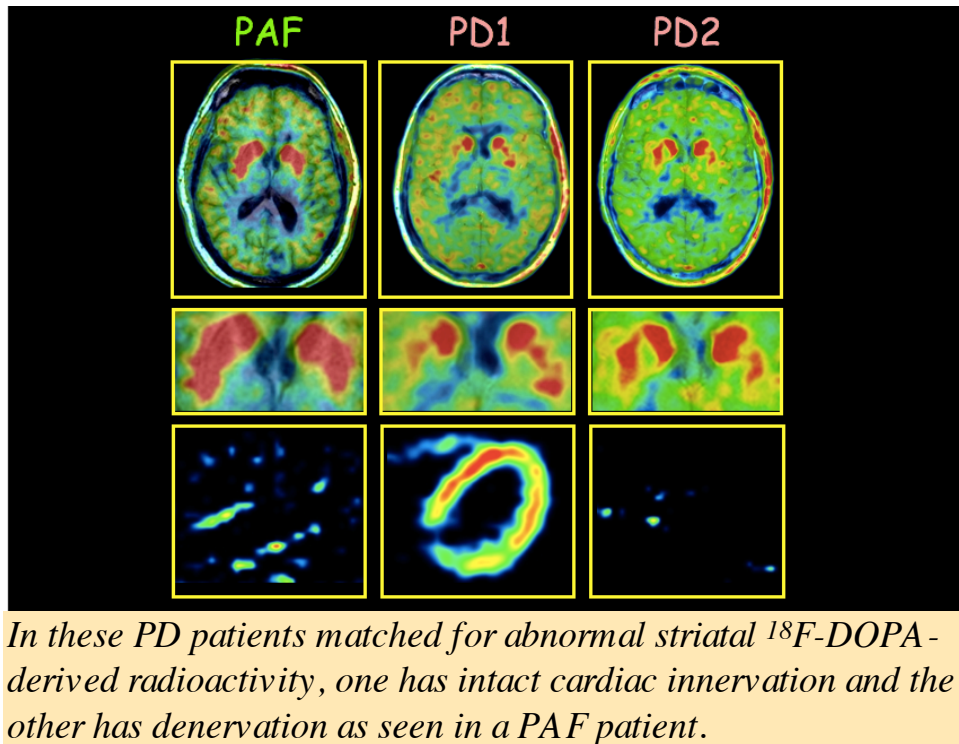
dopamine-derived radioactivity.



This PD patient had normal cardiac sympathetic innervation for several years, followed by a rapid loss, which was first noted in the left ventricular free wall.



In parkinsonian synucleinopathies the extent of the putamen dopaminergic lesion is independent of the extent of the cardiac noradrenergic lesion.



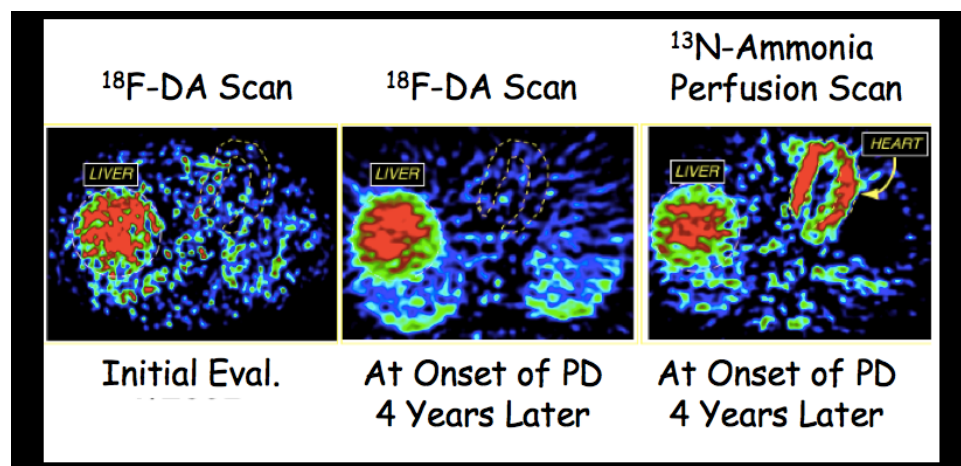
In PD the loss of cardiac sympathetic noradrenergic nerves therefore seems to occur independently of the striatal dopaminergic lesion underlying the movement disorder. In some patients cardiac sympathetic denervation can be a biomarker predicting later development of PD, while in others cardiac sympathetic denervation is a late finding.

A Robot without a Heart

Several years ago, a patient underwent a workup at the NIH Clinical Center for a possible pheochromocytoma, a tumor that produces and releases catecholamines, because he had variable, high blood pressure. The workup was negative, and he was given a diagnosis of “pseudopheochromocytoma.” As part of

the testing the patient had a ^{18}F -dopamine PET scan.

About 4 years later, he returned for testing, this time to be in a study about pheochromocytoma. He reported over the past few months he had noted the gradual onset of slow movement, limb rigidity, a shuffling gait, and decreased facial expression.



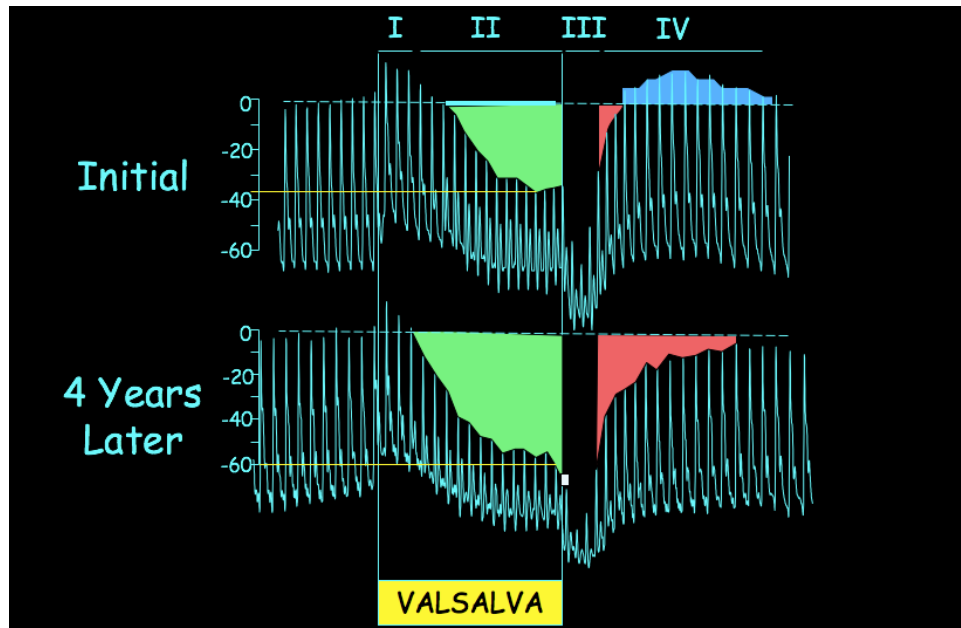
This PD patient had evidence of cardiac sympathetic denervation about 4 years before the motor onset of PD.

He said he felt and looked like a robot. He was diagnosed with PD by a neurology consultant. Cardiac sympathetic neuroimaging by ^{18}F -dopamine PET scanning showed a loss of sympathetic noradrenergic innervation, as is typical of PD.

In retrospect, the ^{18}F -dopamine PET scan from 4 years previously had shown the same loss of sympathetic innervation throughout the left ventricular myocardium.

This was the first reported case of cardiac sympathetic denervation preceding motor signs of PD.

In the interim the patient had also developed baroreflex-cardiovagal and baroreflex-sympathoneural failure, and the beat-to-beat blood pressure response to the Valsalva maneuver now showed a progressive decrease in pressure in Phase II and no overshoot of pressure in Phase IV.



Beat-to-beat blood pressure responses to the Valsalva maneuver in a patient before and after development of motor signs of PD.

DEMENTIA WITH LEWY BODIES

Dementia with Lewy bodies (DLB), or Lewy body dementia (LBD), is a form of alpha-synucleinopathy in which dementia is a key part of the clinical picture. DLB is the second most common form of dementia (the first being Alzheimer's disease).

The Lewy Body Dementia Association uses the term, "Lewy

Body Dementia” to describe two disorders, one of which is DLB and the other PD with dementia. Frankly, I’m confused by this. In the rest of this section I refer to DLB.



Estelle Getty, Robin Williams, and Casey Kasem were celebrities who had dementia with Lewy bodies (DLB).

There are three “core features” for diagnosing DLB: (1) fluctuating cognition, attention, and alertness; (2) visual hallucinations; and (3) parkinsonism. Two of these core features should be present for a diagnosis of *probable* DLB, and one core feature should be present for a diagnosis of *possible* DLB.

There are also three “suggestive features,” and if there is one core feature and in addition a suggestive feature, this switches the diagnosis from possible to probable DLB. The three suggestive features are: (1) dream enactment behavior, as in RBD; (2) severe sensitivity to neuroleptic drugs (drugs used for psychoses such as schizophrenia); and (3) deficient dopamine transporter function in the basal ganglia as demonstrated by SPECT or PET imaging.

Parkinson’s disease with dementia (PD+D) and Alzheimer’s disease are both difficult to separate from DLB. By consensus,

in PD+D, the dementia develops in the setting of PD. Two clinical characteristics may help separate DLB from Alzheimer's disease. The first is visual hallucinations, which occur commonly in DLB. The second is the clinical course. Alzheimer's disease involves a steady, progressive decline, while DLB patients have fluctuating mental status.

Clinical laboratory test that can help distinguish DLB from Alzheimer's disease include neuroimaging tests of catecholamine systems. The finding of decreased putamen ^{18}F -DOPA-derived radioactivity would fit better with DLB than with Alzheimer's disease.

DLB, as all forms of synucleinopathy, often involves a loss of myocardial noradrenergic nerves. Results of cardiac sympathetic neuroimaging may therefore be abnormal in DLB, whereas this is not typically the case in Alzheimer's disease.

I once had a patient who was a retired Professor of physics at a local university. This highly intelligent and educated individual had parkinsonism, orthostatic hypotension, and cognitive impairment. How do you ask such a person if he has hallucinations? I put it this way: "Have you had an experience where you thought were seeing something that really wasn't there or thought you were hearing something that really wasn't there?" Here is how he answered:

"I haven't had any hallucinations—I wouldn't admit to that anyway. I do find my brain to be more creative than it used to be, in filling in the blanks, so to speak. Sometimes you'll see an image, particularly in the distance, not terribly clear, and you think it's one thing, it turns out to be another, but while you're

thinking it's one thing your brain is making it look like that one thing. That phenomenon seems more pronounced to me. I've noticed my peripheral vision sometimes creates illusions, like when I'm driving it seems there's something or someone peripherally when there isn't...but no hallucinations."

Pathologically, DLB is characterized by Lewy bodies distributed widely in the brain. "Diffuse Lewy body disease" is a pathologic diagnosis, whereas DLB is a clinical diagnosis.

The Ironic Case of Dr. Thomas Graboys

Thomas Graboys was one of the cardiology "dream team" who evaluated Reggie Lewis after Lewis had collapsed during an NBA playoff game. Another consultant did a tilt table test and determined that Lewis had merely fainted and could return to playing basketball. Before Lewis ever set foot again on an NBA court, however, he collapsed again—and died. His syncopal episode had not been benign but had been the sign of a serious medical condition.

Graboys wrote a book, *Life in the Balance*, in which he related that on the morning of his second marriage, he had fainted, and he called a cardiologist colleague about it. Before this Graboys, an avid tennis player, had noted episodic lightheadedness or faintness while playing. He also thought he was losing his mental edge. The cardiologist dismissed the problem as mere fainting. Graboys didn't tell his wife about this until later, and this proved to be a major trauma in their marriage.

It turned out that, just as in Reggie Lewis's case, Graboys's

condition was not mere fainting. His episodic lightheadedness and loss of mental edge were actually early symptoms of Parkinson's disease with orthostatic hypotension and Lewy body dementia.



Dr. Thomas Graboys

Graboys was a founding co-president of International Physicians for the Prevention of Nuclear War, which received a Nobel Peace Prize in 1985. He had to retire from his cardiology practice in 2005 and died in January, 2015.

Later you will learn about the “getaway car analogy” for the mechanism of PD. I’d like to introduce the analogy here and end this section with a remarkable quote from Dr. Graboys.

The “getaway car analogy” helps provide answers to four key questions about the pathogenesis of PD. (1) Only a very small fraction of neurons are catecholaminergic. What renders them susceptible to loss in PD? (2) How do generalized abnormalities causing parkinsonism, such as gene mutations, lead to relatively specific loss of catecholamine neurons? (3) Why does alpha-synuclein tend to precipitate in the cytoplasm of catecholamine neurons, in Lewy bodies that are a pathologic hallmark of PD? And (4) Why is PD a disease of the elderly?

To answer these questions, I use the analogy of a bank robber's getaway car. The car is kept in "idle." This has obvious advantages because of the ability to shift into gear rapidly and get away, but there is a cost—cumulative wear and tear.

Catecholamine neurons are like the idling engine of a getaway car. Vesicular catecholamines leak continuously into the cytoplasm, where they are "combusted" by spontaneous and enzyme-catalyzed oxidation. Cytosolic dopamine can be rendered toxic by conversion to the catecholaldehyde 3,4-dihydroxyphenylacetaldehyde (DOPAL). A getaway car has a catalytic converter to deal with byproducts of combustion, and dopamine neurons have an enzyme (enzymes literally are catalytic converters) to detoxify DOPAL. If the enzyme (aldehyde dehydrogenase) were inhibited, then eventually there would be "autotoxicity" (that was funny) caused by DOPAL, and the neurons would die.

In *Life in the Balance*, Graboys wrote as follows about the effects of his disease:

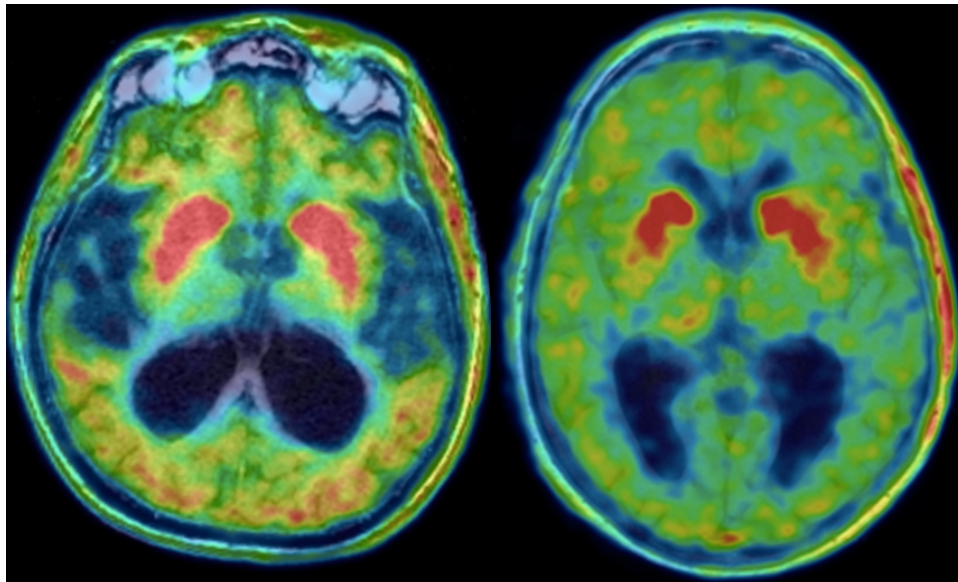
"As a young intern and resident, and later as an attending cardiologist, I was accustomed to being summoned suddenly in the middle of the night. I could launch myself out of bed, get dressed, and perform at my intellectual peak within moments. I could make life-and-death decisions within seconds of a night-time phone call. Today, I wait for thousands of tiny cellular engines to start themselves so I can rise from the bed and begin another day..."

I can't imagine a more poignant reference to the getaway car

analogy for the pathogenesis of Lewy body diseases.

Nature Abhors a Vacuum

One manifestation of dementia in the setting of an alpha-synucleinopathy is shrinkage of the brain and replacement of the brain tissue with fluid. The ventricles and sulci (grooves in the surface of the brain) become enlarged.



Enlargement of the cerebral ventricles and brain atrophy seem to be associated with dementia in PD+OH.

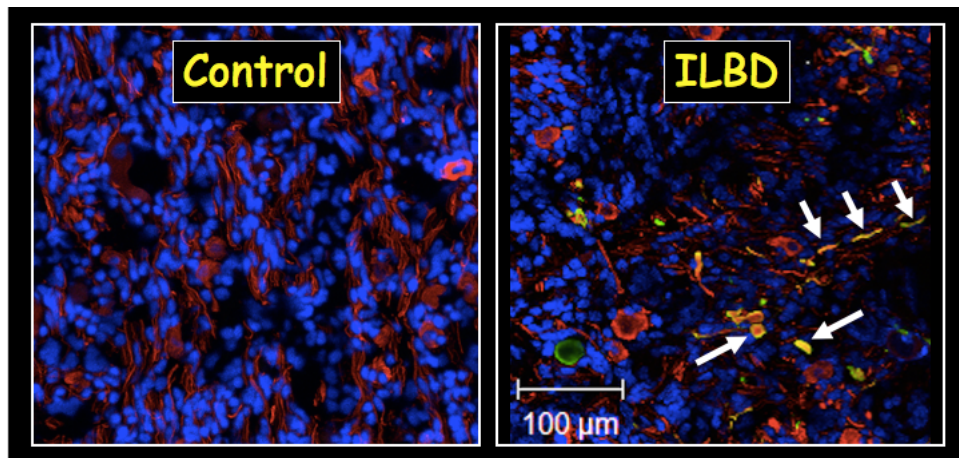
In the body as everywhere else, nature abhors a vacuum, and cerebrospinal fluid in the enlarged cerebral ventricles replaces the lost brain tissue. Sometimes the extent of enlargement of the ventricles is so massive in PD+OH that the clinician considers a diagnosis of normal pressure hydrocephalus. In our experience so far, just about every patient with PD+OH has had enlarged ventricles and cognitive dysfunction.

INCIDENTAL LEWY BODY DISEASE (ILBD)

Lewy bodies can be found in the brain as an incidental finding at the time of autopsy in people who were clinically healthy and did not have parkinsonism or dementia during life. This phenomenon has been called incidental Lewy body disease, or ILBD.

It is possible that Lewy bodies accumulate as part of the normal aging process; however, people with ILBD have an increased amount of loss of substantia nigra dopaminergic neurons and striatal dopaminergic terminals. ILBD might then represent a form of pre-symptomatic PD.

ILBD also involves loss of cardiac sympathetic nerves and deposits of alpha-synuclein in catecholamine fibers in sympathetic ganglion tissue—the “smoking gun” linking synucleinopathy with catecholaminergic neurodegeneration.



Sympathetic ganglion nuclei (blue), TH (red), synuclein (green) and co-localized TH/synuclein (yellow)— “the smoking gun” linking synuclein with sympathetic denervation in ILBD.

AUTOIMMUNITY-ASSOCIATED DYSAUTONOMIAS

There are a variety of dysautonomias where links with autoimmunity have been described. For almost all of these, the exact bases for these links and whether they are causal remain unproven.

It is widely suspected that autoimmunity can cause dysautonomias.

An exception is autoimmune autonomic ganglionopathy (AAG), in which autonomic failure results from circulating antibodies to the neuronal nicotinic receptor.

There is a rather prevalent view among patients and support groups that dysautonomias such as POTS have an autoimmune basis. Research to test this idea is ongoing. Some clinicians have tried intravenous immunoglobulin (IVIG) to treat patients who have acute or subacute onset of POTS or autonomically mediated syncope.

As of this writing, however, the only form of dysautonomia in which strong evidence for an autoimmune mechanism has been obtained is AAG.

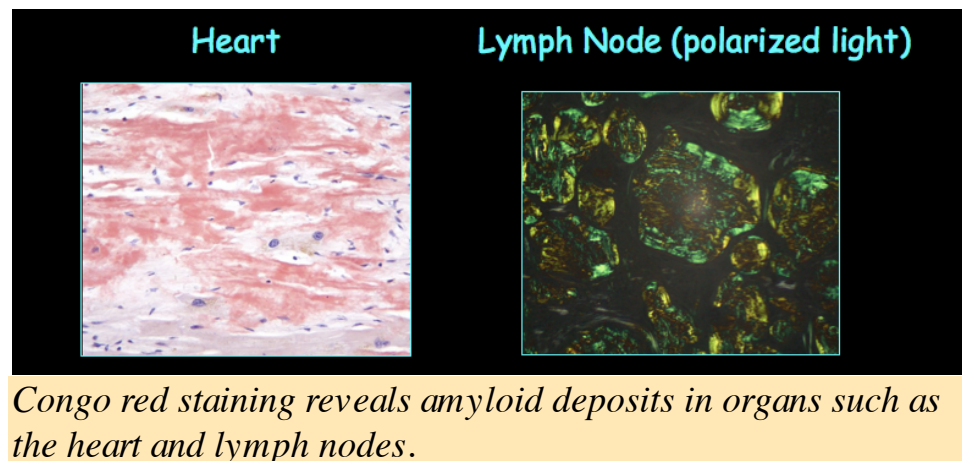
Amyloidosis

Amyloidosis refers to a variety of disorders that have in common deposition of a mis-folded protein called amyloid in

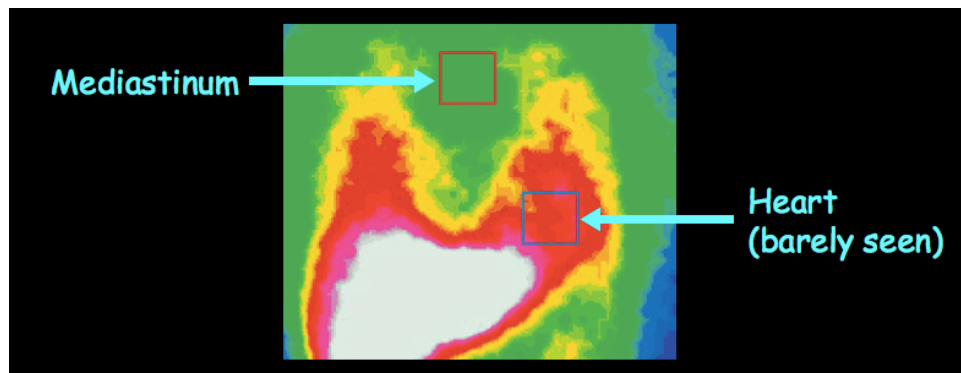
body organs. Normally the protein is soluble, but the misfolding causes the protein to precipitate. The disease manifestations depend on the organs involved—especially the heart and kidneys.

Amyloidosis can involve the sensory and autonomic fibers in peripheral nerves. Peripheral neuropathy in amyloidosis is usually symmetrical. I remember a case of amyloid-associated autonomic failure where the patient wore gloves continuously, even in his hospital bed at the NIH Clinical Center, in an effort to decrease his distressing “pins and needles” sensations.

One can diagnose amyloidosis by biopsy of mucus membranes (rectal, buccal) or abdominal fat pad tissue, looking for deposits of the amyloid material. Congo red staining, combined with polarized light, demonstrates the proteins microscopically.



Patients with amyloidosis can have marked reduction in cardiac sympathetic noradrenergic nerves, as indicated by cardiac sympathetic neuroimaging.

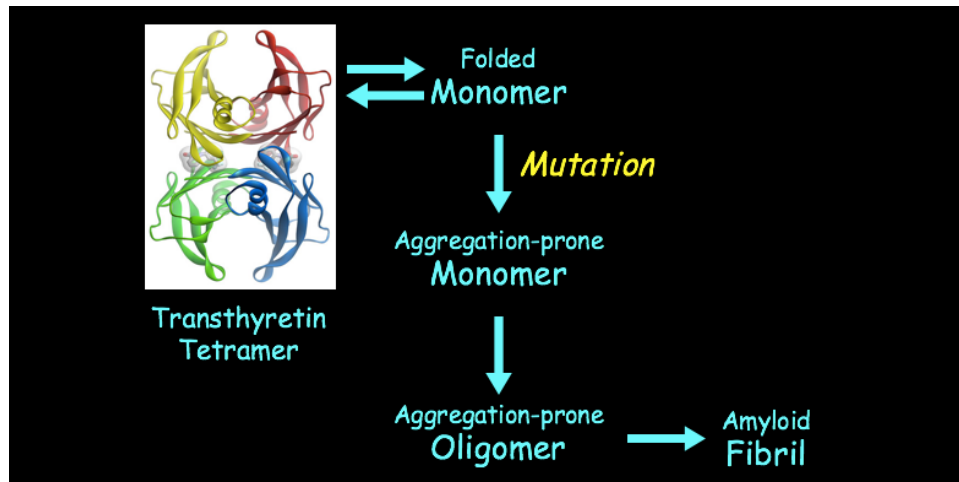


¹²³I-MIBG scan showing amyloidosis-associated cardiac sympathetic denervation. The heart should appear white, like the liver.

HEREDITARY TRANSTHYRETIN AMYLOIDOSIS

Hereditary transthyretin amyloidosis is a rare but clinically and scientifically important cause of chronic autonomic failure. It is important clinically, because if left untreated the disease progresses to lethality at a young age, and correct diagnosis and timely treatment can prolong life. It is important scientifically, because the disease seems to exemplify a class of progressive neurodegenerative disorders that are associated with abnormal deposition of proteins, analogous to alpha-synuclein in Parkinson's disease and tau in progressive supranuclear palsy.

In other diseases the pathogenic role of the abnormal protein is a matter for research, but in hereditary transthyretin amyloidosis there is no doubt. The disease results from extracellular deposition of the mutated protein, transthyretin (TTR), in a variety of organs and tissues—especially the liver, heart, gut, and peripheral nerves.



Pathogenetic schema relating transthyretin gene mutation to familial amyloidotic polyneuropathy

Normally TTR exists as a tetramer, but the abnormal protein tends to dissociate to monomers that misfold and aggregate to form insoluble fibrils.

When presenting mainly as sensory, autonomic, and motor polyneuropathy, the term familial autonomic polyneuropathy (FAP) has been used, and when presenting mainly as cardiomyopathy, familial amyloid cardiomyopathy (FAC) has been used. A mixed form also can occur. The disease is transmitted as an autosomal dominant trait.

FAP at first predominantly involves small unmyelinated nerve fibers and manifests with sensory loss mainly affecting pain and temperature sensation. Later, involvement of motor fibers causes progressive weakness and gait abnormalities.

The amyloid fibrils are extracellular, and the neurotoxic

mechanism producing length-dependent polyneuropathy in FAP is poorly understood. It has been proposed that mutated TTR exerts adverse effects at neuronal cell membranes.

In the central nervous system, amyloid is found in the choroid plexuses and around blood vessels—cerebral amyloid angiopathy. Although there is no intra-neuronal amyloid deposition, there are diffuse metabolic changes in brain that may be related to axonal damage.

In FAC the cardiomyopathy involves amyloidotic infiltration of the myocardium, arrhythmias or heart block, and autonomic denervation. A major feature of FAC is cardiac dysautonomia, which is associated with worse survival.

The exact mechanisms of amyloid-related autonomic failure are unknown. There is no known effective treatment for autonomic neuropathy in the setting of amyloidosis.

Sjogren's Syndrome

Sjogren's syndrome is a condition in which the patients have chronically dry mouth and dry eyes, typically in the setting of some form of connective tissue disease like rheumatoid arthritis. There is evidence of autoimmunity directed against the salivary glands and lacrimal glands, with infiltration of the tissue by lymphocytes.

The vast majority of Sjogren's syndrome patients are adult women—just as is the case for postural tachycardia syndrome, autonomically mediated syncope, chronic fatigue syndrome,

temperomandibular joint disorder, and migraine. One of the most famous patients with the condition is the professional tennis player, Venus Williams. She has reported chronic fatigue associated with her Sjogren's syndrome. Since having to drop out of the US Open in 2011, she has returned to close to her former performance, with a vegan diet and exercise regimen.



The professional tennis player, Venus Williams, had to drop out of the US Open in 2011 due to fatigue related to Sjogren's syndrome.

Sjogren's syndrome has long been suspected of involving a form of dysautonomia. A recent report suggested dysfunction of the parasympathetic cholinergic system; however, sympathetic noradrenergic nervous system function seems intact.

Guillain-Barré Syndrome

Guillain-Barré syndrome is a condition in which there is

autoimmune attack on peripheral nerves. The syndrome often follows by a few days or weeks a respiratory or gastrointestinal viral infection or surgery. The target tissue is the myelin sheath surrounding nerves or the nerve fibers themselves. The longer nerves are affected earlier, explaining initial findings in the feet or hands, with a centripetal progression. The symptoms and signs are of an ascending symmetric weakness or paralysis and altered sensation beginning in the feet and moving upwards in the body. The patient's clinical status declines over the course of hours to days to weeks, with the condition at its worst after a few weeks. In severe cases the patient becomes totally paralyzed and can die from respiratory failure. Eventually the patient recovers, although there can be residual weakness.

Andy Griffith, who played the beloved sheriff of Mayberry in the hit television series bearing his name, died of a heart attack in 2012. At the time few realized that he had suffered from Guillain-Barré syndrome for many years.



Andy Griffith, who received a Presidential Medal of Freedom in 2005, suffered from Guillain-Barré syndrome.

The sequence of clinical events in his case was rather typical. He had flu-like symptoms, and when these began to clear, searing pain came on along with inability to feel his legs. He

collapsed from the pain and subsequently developed spreading muscle weakness and paralysis.

He did not develop respiratory failure. He underwent nearly a year of convalescence, and he was left with a permanent limp. For a time, he wore plastic leg braces, but discarded them “because they squeaked and the soundman could hear them.”

Treatment of Guillain-Barré syndrome includes, plasma exchange (plasmapheresis) and high-dose intravenous immunoglobulin (IVIG).

Large swings in blood pressure, tachycardia, abnormal heart rhythms, and altered sweating can accompany Guillain-Barré syndrome. These abnormalities suggest involvement of multiple components of the autonomic nervous system, with parasympathetic nervous failure and activation of the sympathetic noradrenergic and adrenergic systems.

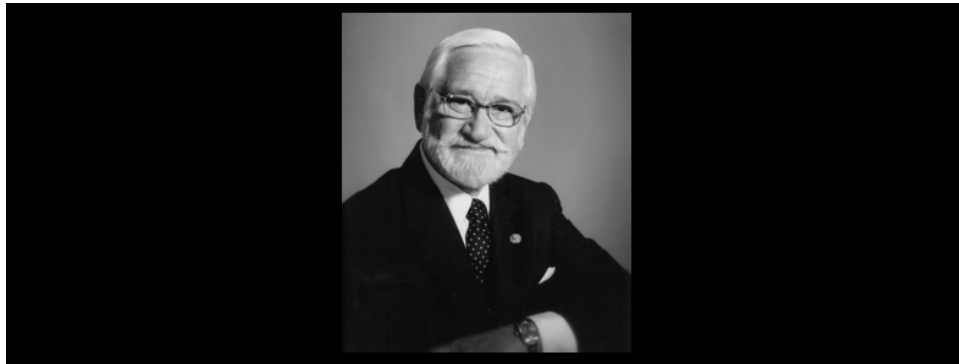
Guillain-Barré syndrome patients can develop a form of reversible heart failure that may be mediated by catecholamines. The condition resembles *takotsubo* cardiopathy.

THE SABIN AFFAIR

Another famous person who may have had Guillain-Barré syndrome was Dr. Albert B. Sabin, the developer of the oral polio vaccine.

During World War II Sabin had conducted research on

infectious polyneuritis in soldiers. In 1941 he was the first author of a report published in *The American Journal of Pathology*, entitled, “Visceral lesions in infectious polyneuritis (infectious neuronitis, acute polyneuritis with facial diplegia, Guillain-Barré syndrome, Landry’s paralysis).”



Albert Sabin, developer of the oral polio vaccine

More than 40 years later, in the early 1980s, and long after having attained international renown for developing the oral polio vaccine, Sabin conducted experimental therapeutic trials of an aerosolized measles vaccine in Brazil and Mexico. Not only did the vaccine not work, but he also contracted a syndrome manifested at first by weak and wobbly legs. After studying paralyzing viral diseases for more than a half century, he himself seems to have come down with a form of post-viral paralysis.

He was diagnosed with a rare cervical spine disease in which a ligament bordering the spinal canal becomes bony. He underwent neurosurgery for this and did have transient relief, but this was followed about two months later by the sudden onset of severe leg pain and ascending paralysis. He lost control of his legs, then his arms, developed pneumonia, and

had an episode of respiratory arrest, which an aide in attendance happened to notice; her alerting medical personnel saved his life. He attributed his condition to a side effect of the neurosurgery and his cessation of breathing to obstruction of his endotracheal tube.

The pain and paralysis lasted several months more. A patient at the NIH Clinical Center for rehabilitation therapy, he slowly regained function of his arms and upper body. In a news article he was quoted as saying, “Maybe I’ll walk again...I expect to. I’m regaining some powers, fiber by fiber.” In June of that year he gave a half hour talk on viral diseases at the NIH — while standing. By July of 1984 he could walk briefly without a cane, but with an obvious wobble. He died of heart failure in 1993 at the age of 86.

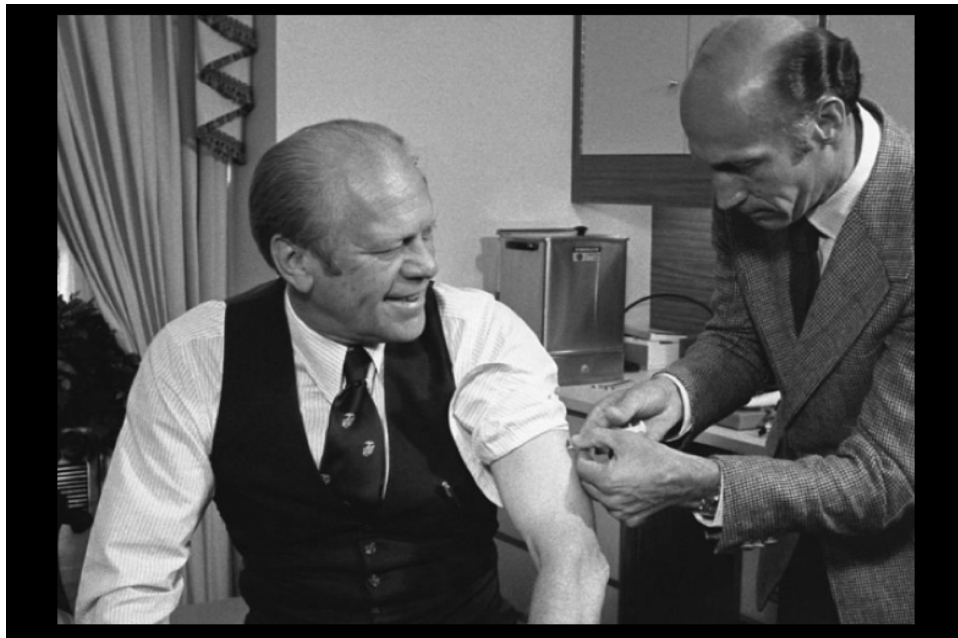
THE SWINE FLU AFFAIR

In January, 1976 an outbreak of H1N1 “swine flu” virus broke out among Army recruits in Fort Dix, NJ. Because of similarity of the viral strain to that involved in the influenza pandemic in 1918, a massive immunization campaign began. More than 40 million Americans received the vaccination.

When then US President Gerald Ford flew Albert B. Sabin to the White House to help publicize the swine flu vaccination program, Sabin gave the blunt opinion, “I said the whole program was unfounded...There was no basis for vaccinating everybody.” The campaign went ahead anyway.

There were disastrous consequences. About 2,000 people were

left permanently paralyzed. About 500 lawsuits against the US Government (corresponding to about \$4 billion) were filed related to Guillain-Barré syndrome as a result of the vaccine. A few months later the US Government stopped the swine flu immunization campaign, because of the cases of Guillain-Barré syndrome.



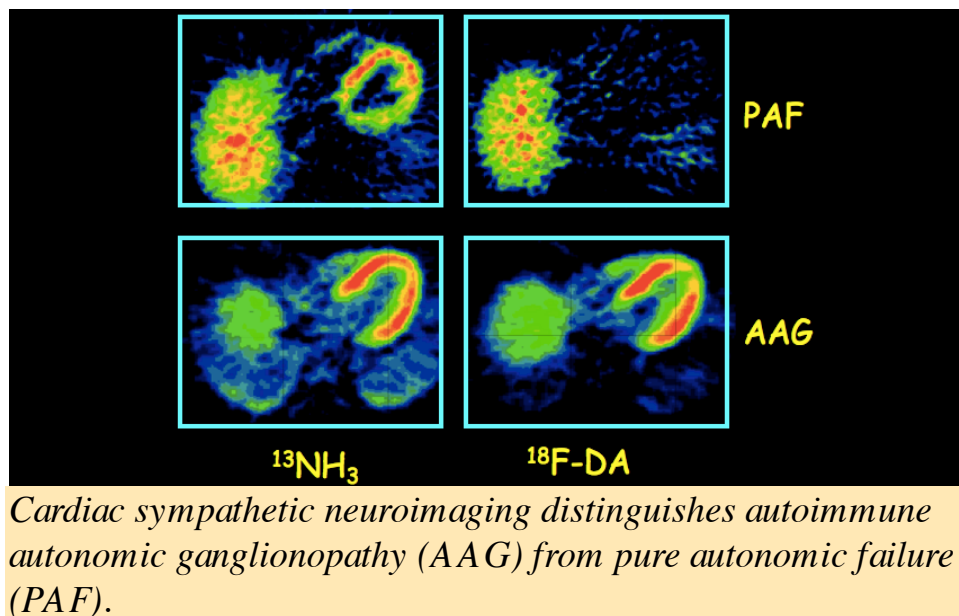
President Gerald Ford receives the swine flu vaccination.

Since about 40 million people received the vaccine, the risk of Guillain-Barré syndrome, while increased, was extremely small. In 2003 the US Institute of Medicine concluded that there was evidence for a causal relationship between the 1976 swine flu vaccination campaign and Guillain-Barré syndrome in adults.

The Old Lady Who Couldn't Spit

Several years ago, at the NIH Clinical Center I evaluated an elderly African-American resident of the District of Columbia for severe orthostatic hypotension. She had orthostatic intolerance, but this was not her chief complaint. Her chief complaint was that she couldn't make spit.

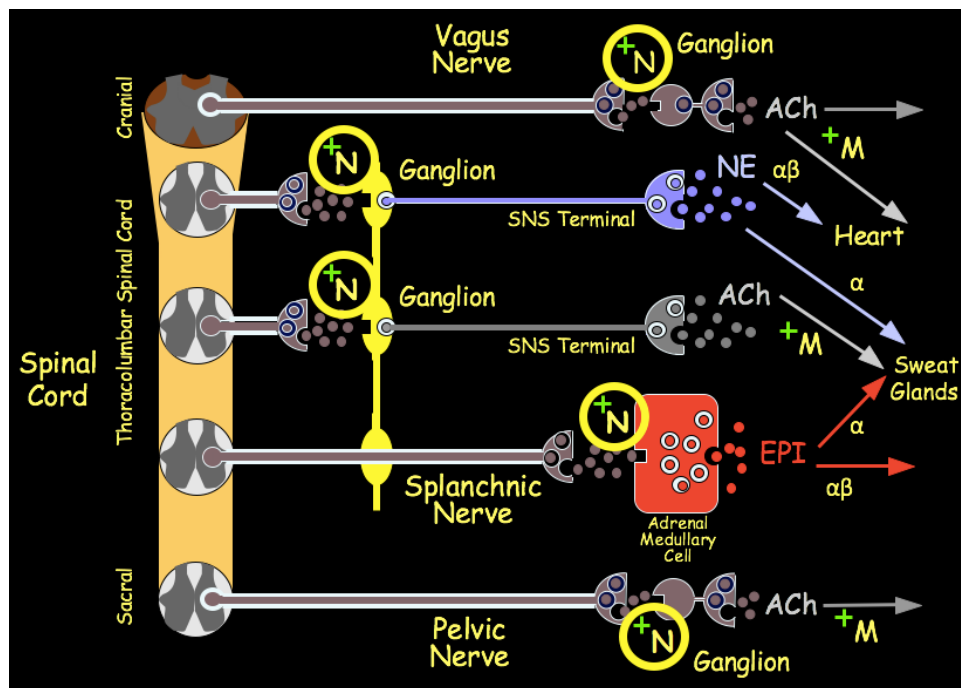
Her mouth was so dry, she couldn't chew food. She was also severely constipated. The combination of not being able to salivate and having severe constipation had resulted in her becoming malnourished. When first seen, she looked cachexic, like a concentration camp survivor or a patient with end-stage cancer.



She had characteristic abnormalities of beat-to-beat blood pressure associated with the Valsalva maneuver, indicating that

her orthostatic hypotension was not from dehydration but from a neurogenic cause. She also had an extremely low plasma norepinephrine level. Initially I thought she had pure autonomic failure (PAF) and predicted that her ^{18}F -dopamine PET scan would show loss of sympathetic innervation of the heart.

Instead, her ^{18}F -dopamine PET scan was normal. Moreover, under the study protocol she received a ganglion blocker, and this produced hardly any effects at all.



Because of the role of the nicotinic cholinergic receptor in autonomic neurotransmission, autoimmunity to the receptor results in a pandysautonomia.

At about that time Dr. Steven Vernino had published a study about autoimmune autonomic neuropathy associated with a circulating antibody to the neuronal nicotinic receptor, which

mediates ganglionic neurotransmission. No patient with PAF had such an antibody; I suspected our patient might and sent Dr. Vernino a sample, which was positive. Together we published the first case of what has come to be known as autoimmune autonomic ganglionopathy (AAG).

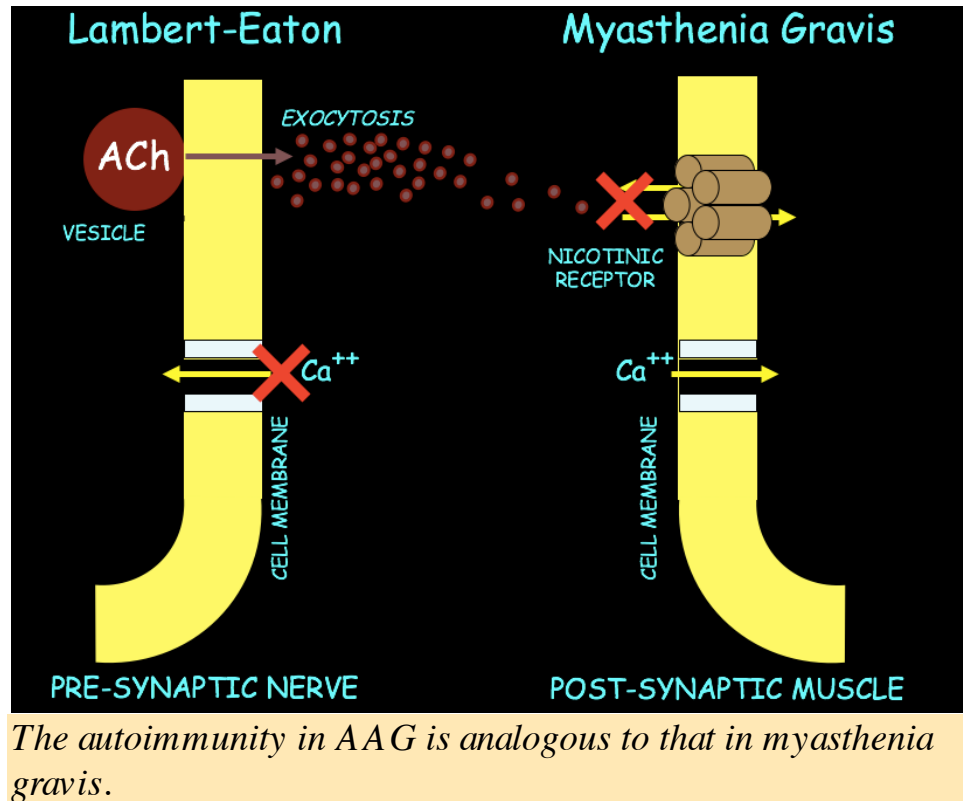
AAG has turned out to be quite a rare form of acquired autonomic failure in which there is decreased activity of all the components of the autonomic nervous system—pandysautonomia. The pandysautonomia results from circulating antibodies to the neuronal form of the nicotinic acetylcholine receptor (nAChR).

The antibodies interfere with ganglionic neurotransmission, and so post-ganglionic nerve traffic is decreased in the parasympathetic nervous system and the sympathetic noradrenergic and cholinergic systems.

AAG manifests with symptoms and signs of decreased post-ganglionic neurotransmission. Because of parasympathetic cholinergic failure, the patient has decreased salivation, lacrimation, gastrointestinal movements, and bladder tone. Because of sympathetic cholinergic failure, the patient has decreased sweating. Because of sympathetic noradrenergic system failure, the patient has neurogenic orthostatic hypotension.

Myasthenia gravis also involves autoimmunity to nicotinic receptors, but these mediate neuromuscular transmission and have different components from the nicotinic receptors mediating autonomic transmission. The closely related Lambert-Eaton syndrome involve autoimmunity to calcium

channels rather than nicotinic receptors.



Since the lesion in AAG is at the level of the neuronal nicotinic receptor, there is no reason to suspect that the neurogenic orthostatic hypotension reflects loss of post-ganglionic sympathetic noradrenergic nerves. On the other hand, interference with ganglionic neurotransmission would result in decreased post-ganglionic sympathetic nerve traffic. This explains the combination of low plasma norepinephrine levels with normal cardiac sympathetic neuroimaging results in AAG.

Plasma levels of DHPG, the main neuronal metabolite of norepinephrine, provide a better index of sympathetic noradrenergic innervation than do levels of norepinephrine

itself. In AAG, plasma norepinephrine levels are lower than expected for DHPG levels, presumably because of decreased exocytotic release from generally intact post-ganglionic sympathetic nerves.

To treat the patient's chief symptom, dry mouth, we prescribed bethanechol (Urecholine™), which is a muscarinic cholinergic agonist. Bethanechol treatment produced a very gratifying result in our patient—she had a return of her ability to make saliva, alleviating her chief complaint.

Management of AAG usually focuses on anti-autoimmune therapies with plasma exchanges (to remove the circulating antibodies to the neuronal nicotinic receptor), steroids, rituximab (a drug that is toxic to antibody-producing B cells), or mycophenolic acid (Cellcept™). The long-term outlook in AAG is unknown.

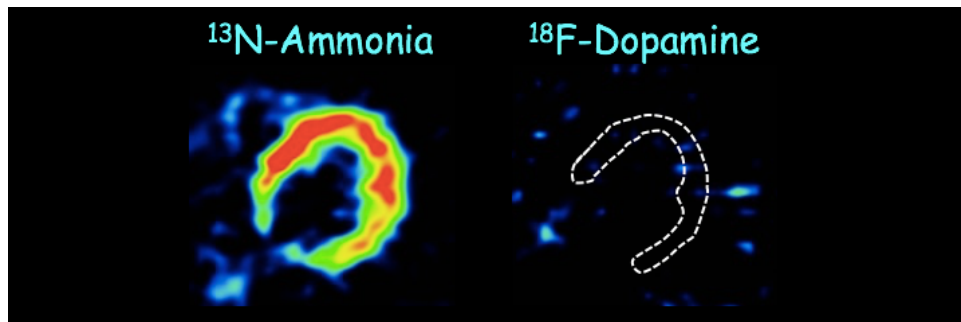
Autoimmunity-Associated Autonomic Denervation

Autoimmunity-associated autonomic failure can reflect a post-ganglionic lesion, in contrast with a ganglionic lesion as seen in AAG.

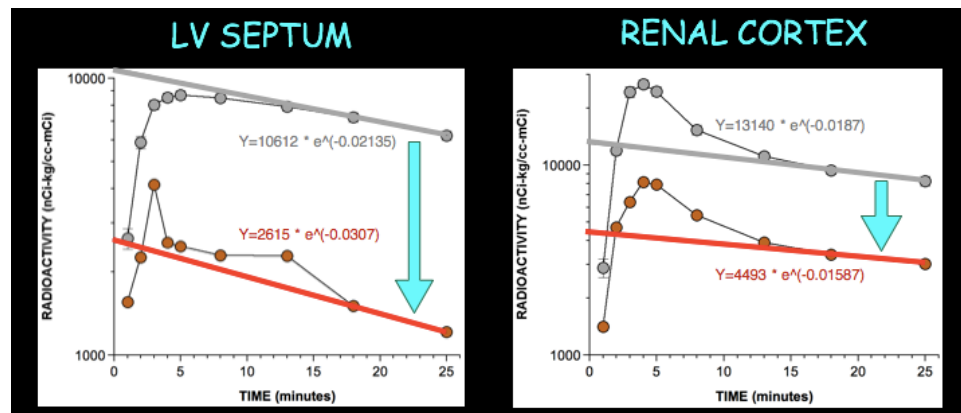
Autoimmunity-associated autonomic denervation (AAD) seems to manifest first with a pandysautonomia, followed by relatively more rapid recovery of parasympathetic than of sympathetic functions. This sequence suggests that the target of autoimmune attack is post-ganglionic, unmyelinated axons, because parasympathetic post-ganglionic axons are short and

may regenerate quickly, whereas sympathetic post-ganglionic axons are long and may regenerate slowly and incompletely.

Analysis of ^{18}F -dopamine scanning data suggests that AAD involves loss of sympathetic noradrenergic nerves supplying the kidneys as well as the heart.



Cardiac sympathetic denervation revealed by ^{18}F -dopamine scanning in a patient with autoimmunity-associated autonomic denervation.



Decreased ^{18}F -dopamine-derived radioactivity in the heart and renal cortex in a patient with AAD (red) compared to controls (gray) There is evidence of cardiac and renal sympathetic denervation.

OTHER DYSAUTONOMIAS

SUNCT

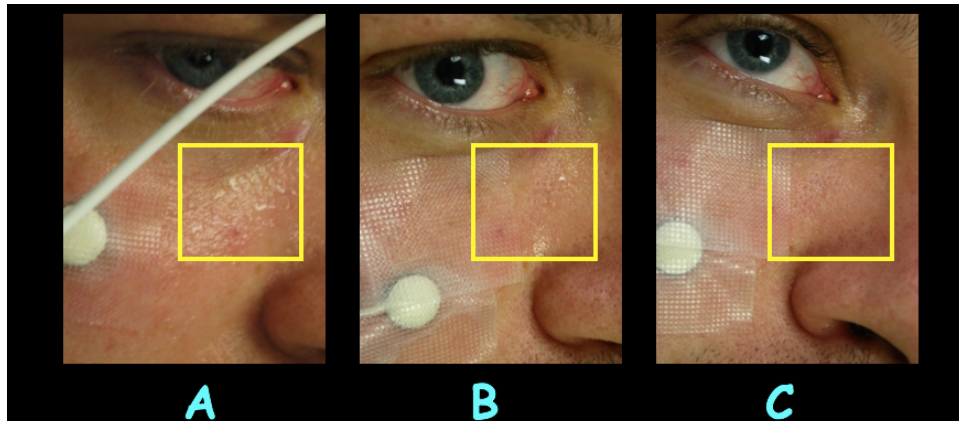
The abbreviation, SUNCT, stands for short-lasting unilateral neuralgiform headache with conjunctival injection and tearing. As the name implies, this syndrome involves episodic painful headache, especially in the area of the eye, with conjunctival injection and tearing on the affected side.

The condition occurs most frequently in adult men. SUNCT is rare, and mechanisms of SUNCT are poorly understood. SUNCT is among a group of headaches called trigeminal autonomic cephalalgia, because the nerve fibers supplying the affected regions travel with the trigeminal nerve, the fifth cranial nerve.

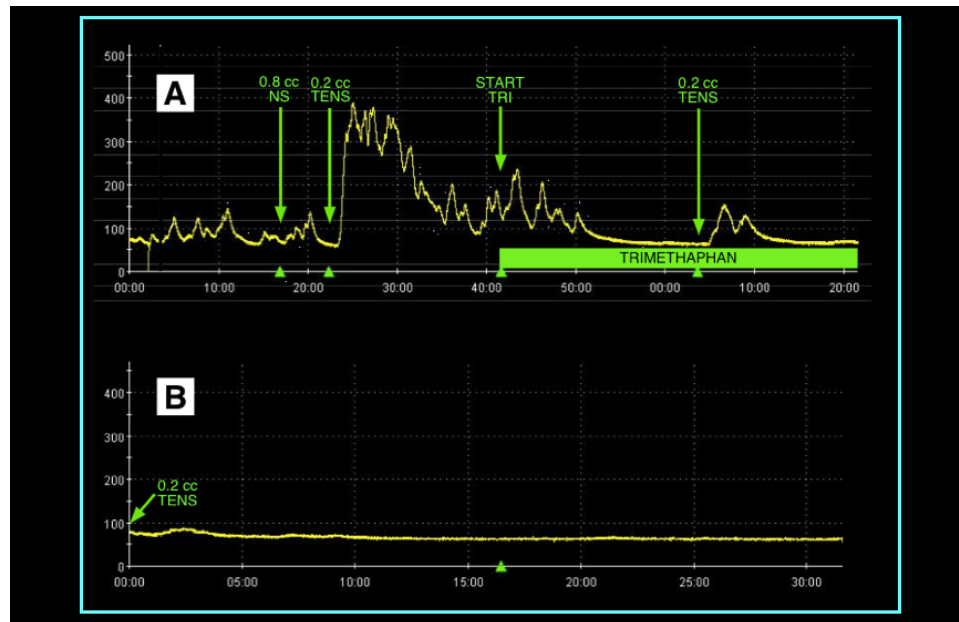
SUNCT attacks typically last from 5 seconds to 4 minutes per episode, and patients can have 5-6 attacks per hour. There is no known effective treatment. Corticosteroids, gabapentin, and anti-epileptic drugs have been tried.

Several years ago I evaluated a patient who had attacks of severe pain in the head and face accompanied by conjunctival injection, nasal stuffiness, and local sweating. Injection of edrophonium (Tensilon™), which blocks acetylcholine metabolism, evoked an attack, and ganglion blockade with trimethaphan prevented the Tensilon effects. These findings indicated that the acetylcholine released from autonomic nerves mediated the attacks.

In retrospect, the patient may have had a form of SUNCT;
however, his condition was bilateral.



Conjunctival injection, tearing and peri-orbital and forehead sweating accompanying pain evoked by edrophonium.



Prevention of edrophonium-induced sweating and pain by ganglion blockade with trimethaphan. (A) and (B) are continuous recordings of forehead humidity.

Harlequin Syndrome

This dramatic but rare syndrome involves the sudden onset of facial flushing and sweating on one side of the head after exercise or heat exposure. The cause is disruption of sympathetic nerve fibers, which ascend in the chest and neck alongside the carotid artery.



Examples of harlequin syndrome

The flushing and sweating occur on the side opposite the sympathetic lesion, presumably because of a form of compensatory activation of the intact sympathetic pathway. The affected side remains relatively dry and pale.

Rarely, Horner's syndrome and the harlequin syndrome occur together; when this happens the ptosis and miosis occur on the same side as the lesion, while the flushing and sweating occur on the opposite side.

Erythromelalgia

The term, “erythromelalgia,” comes from the Latin for red, painful extremities. The images below convey graphically the main visible changes in this rare condition.



Examples of erythromelalgia.

Patients with erythromelalgia have redness, swelling, and an intense burning sensation in the extremities or face. The symptoms worsen with exposure to heat or exercise and are relieved by local cooling of the skin.

Secondary forms of erythromelalgia are associated with other conditions, such as myeloproliferative diseases, autoimmune disorders, Fabry disease, or hypercholesterolemia, or drugs, such as fluoroquinolones (a class of antibiotics), bromocriptine (a dopamine receptor blocker), pergolide (a dopamine receptor

agonist), verapamil (a calcium channel blocker), and ticlopidine (an anti-platelet drug). Mechanisms of secondary erythromelalgia are poorly understood.

Primary erythromelalgia usually has no known cause. Rarely, primary erythromelalgia is inherited as an autosomal dominant trait, results from hyperexcitability of nociceptor C-fibers in the dorsal root ganglion. The dorsal root ganglion neurons relay pain impulses to the spinal cord. The hyperexcitability typically results from mutation of the gene encoding a subunit of the voltage-gated sodium channel, *NA(v)17*. The channels are activated at more hyperpolarized trans-membrane electrical potentials than normal, so that the channels are open for prolonged periods.

The striking red skin coloration reflects excessive local accumulation of blood. The skin feels warm. Elevation of the affected extremity temporarily reverses the redness. Why the blood accumulates remains mysterious.

Sympathetic neurons in ganglia express the same *NA(v)17* channel; however, whether erythromelalgia involves abnormal sympathetic neurocirculatory regulation is poorly understood. Between flare-ups, under resting conditions microcirculatory flow is decreased, and there is blunting of reflexive responses of microcirculatory flow to the Valsalva maneuver and cooling of the opposite extremity. These abnormalities have been interpreted in terms of decreased cutaneous perfusion combined with reflexive sympathetically mediated vasoconstriction, due to small fiber sympathetic neuropathy and denervation hypersensitivity; however, only a small minority of erythromelalgia patients have small fiber sympathetic

neuropathy based on analyses of skin biopsies.

Patients with erythromelalgia wish to stay in a cool environment. Patients I have seen have brought with them small fans to blow against their skin. The condition can be socially isolating and depressing. I had a patient who had no complaints dunking her feet in ice cold water. This should not be used as a form of treatment, however, because of damage to the skin.

There is no known consistently effective treatment of erythromelalgia. Tramadol, amitriptyline, mexiletine (a non-selective voltage-gated sodium channel blocker), or opioids may give relief.

MANAGING DYSAUTONOMIAS

OVERVIEW

Successful management of a dysautonomia involves more than obtaining a correct diagnosis and then instituting curative treatment. Even at the most sophisticated and knowledgeable centers, the diagnosis often remains uncertain, especially for functional disorders. An agreed upon diagnosis, such as postural tachycardia syndrome, does not necessarily carry with it agreed upon ideas about the mechanism of the condition, the most appropriate treatment, or the long term outcome.

Expecting “cures” for dysautonomias is unrealistic.

On the other hand, there are many treatments for dysautonomias, including non-drug and drug treatments, and there are many coping tactics. This section focuses on these aspects of autonomic medicine.

TREATMENT OF DYSAUTONOMIAS

The Most Effective Treatments

The most effective treatment of dysautonomias is education.

Effective management includes learning about situations likely to worsen or improve symptoms. Joining a support group, you can compare notes with others in the same situation and “flip the clinic” by educating clinicians about individual experiences. You also benefit fellow patients and humanity in general by participating in research and in helping train physicians.

Often the most effective treatment for a dysautonomia is time. For instance, postural tachycardia syndrome that comes on soon after a viral infection in an otherwise healthy person may “melt away” over many months or years.

Another often effective treatment is exercise, for a few reasons. First, in patients with chronic orthostatic intolerance, maintaining excellent muscle tone in the anti-gravity muscles of the buttocks, thighs, and calves maximizes the efficiency of muscle pumping to maintain venous return to the heart during orthostasis. Second, exercise training improves the ability to increase cardiac output. Third, it is important in chronic, debilitating disorders for the patient to regain a sense of at least some control over the situation.

Non-Drug Treatments

Several non-drug treatments are used for different types of dysautonomias. The rationale for a treatment depends on the dysautonomia. Sometimes the responses of a patient to a treatment help the doctor determine the diagnosis. Patients with dysautonomias can feel differently from day to day, without any clear reason why. This means that if a treatment is tried, it may take a trial period to decide whether the treatment has helped or not.

ELEVATION OF THE HEAD OF THE BED



Elevation of the head of the bed is a non-drug treatment for orthostatic hypotension and supine hypertension.

In patients who have a fall in blood pressure every time they

stand up (orthostatic hypotension), elevation of the head of the bed on blocks at night improves the ability to tolerate standing up in the morning.

SALT INTAKE

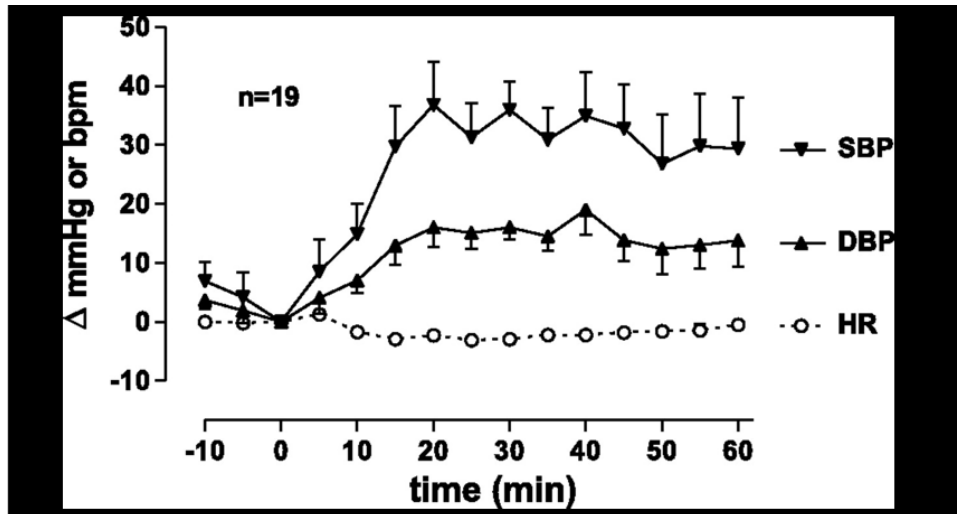
High salt intake tends to increase the volume of fluid in the body. A small percent of this volume is in the bloodstream. Doctors usually recommend a high salt diet for patients with an inability to tolerate prolonged standing (chronic orthostatic intolerance) or with a fall in blood pressure during standing (orthostatic hypotension).

Normally when a person takes in a high salt diet, the kidneys increase the amount of salt in the urine, and this limits the increase in blood volume. After a few days of the same salt intake, the rate of sodium excretion equals the rate of intake. Drugs that promote retention of sodium by the kidneys, such as fludrocortisone, are usually required for high salt intake to increase body fluid volume effectively.

WATER DRINKING

A relatively recently described tactic to increase blood pressure in patients with autonomic failure is to drink 16 ounces of water. Why water drinking should increase the blood pressure in patients with autonomic failure, when doing so does not affect the blood pressure of healthy people, remains unclear. Researchers have proposed the existence of an “osmopressor response,” in which ingested water without solute acts in the gut or liver to increase sympathetic noradrenergic system

outflow at the level of the pre-ganglionic neurons in the spinal cord. The sensors evoking the response are still unknown.



The osmopressor response to ingesting 16 ounces of water.

The osmopressor response may improve orthostatic tolerance in patients with baroreflex failure or autonomically mediated syncope.

Patients with chronic orthostatic intolerance, autonomically mediated syncope, or POTS often keep a water container with them and sip from it repeatedly during the day. This habit might indicate a tendency to dehydration and low blood volume, but the pathophysiologic meaning of the “water bottle sign” remains unclear.

MEALS

Eating a big meal leads to shunting of blood toward the gut. In people with dizziness or lightheadedness when they stand up

(orthostatic intolerance), it is usually advisable to take frequent small meals.

Reducing the amounts of sugars or other carbohydrates in meals may help manage symptoms.

A substantial proportion of patients with chronic orthostatic intolerance have gastrointestinal symptoms and signs leading to a diagnosis of gastroesophageal reflux, slowed gastric emptying, or irritable bowel syndrome. Gastroenterologists managing these patients should be aware that recommending a high fiber diet might worsen orthostatic intolerance by augmenting shunting of blood to the gut.

COMPRESSION HOSE/ABDOMINAL BINDER

Compression hose or other compression garments tend to decrease the amount of pooling of blood in veins when a person stands. This can decrease leakage of fluid from the veins into the tissues and decrease swelling of the feet. In patients with veins that fill up or leak excessively during standing, compression garments can improve toleration of prolonged standing. In POTS patients a “step-in” abdominal binder may be more efficient than compression stockings, by limiting orthostatic blood pooling in the abdomen and pelvis.

In patients with a fall in blood pressure during standing (orthostatic hypotension, OH), the problem may be less with the veins than with the arteries and arterioles, the blood vessels that carry oxygen-rich blood under high pressure to the organs and limbs. Wearing compression hose may be disappointing in the

management of orthostatic hypotension.

Because of the baroreflex failure attending OH from chronic autonomic failure, decreases in venous return to the heart are directly translated into decreased blood pressure. When a person stands up, blood tends to pool in the abdomen. Inflation of an abdominal binder (which resembles a huge blood pressure cuff) squeezes blood out of the abdomen and increases venous return to the heart. An automated abdominal binder is under development to mitigate OH in patients with chronic autonomic failure.

COFFEE

Some patients with dysautonomias feel better drinking caffeinated coffee frequently. Others feel jittery or anxious and avoid caffeinated coffee. Still others notice no effect.

TEMPERATURE

Patients with dysautonomias often have an inability to tolerate extremes of environmental temperature. When exposed to the heat, patients with failure of the sympathetic cholinergic system may not sweat adequately to maintain the core temperature by evaporation of the sweat. Patients with chronic orthostatic intolerance, such as from postural tachycardia syndrome (POTS), can have heat intolerance because of loss of blood volume by sweating or shunting of blood away from the brain. When exposed to cold, patients with sympathetic noradrenergic system failure may not constrict blood vessels adequately in the skin, so that the body temperature falls (hypothermia).

EXERCISE

Patients with dysautonomias sometimes benefit markedly from an individualized exercise training program. Often, however, the training does not eliminate the sense of fatigue. It might help to have small amounts of exercise daily, even for only 5-10 minutes. A formal online program was available at the University of Texas Southwestern Medical Center as part of a clinical research study, but the study ended.

As a person exercises, the blood vessels carrying oxygen-rich blood to the exercising muscle (arteries and arterioles) tend to relax, due to the accumulation of byproducts of metabolism. Reflexive stimulation of the sympathetic noradrenergic system normally counters this tendency by increasing the tone of the blood vessel walls. The blood flow to the exercising muscle therefore is in a dynamic state of balance. Activation of sympathetic nerves to the heart during exercise increases the force and rate of the heartbeat and the total amount of blood pumped by the heart in one minute (cardiac output). Meanwhile, like squeezing a tube of toothpaste, pumping of muscle during exercise increases the movement of blood from the limbs back to the heart. The increased metabolic activity tends to increase body temperature, and sweating, which is stimulated importantly by sympathetic cholinergic nerves to sweat glands. Sweating increases the loss of heat by evaporation, helping maintain the core temperature.

If a patient had failure of the sympathetic noradrenergic system, excessive production of byproducts of metabolism, or a form of

heart disease involving decreased ability to increase the force or rate of the heartbeat, then the blood pressure could fall during exercise and produce a sense of fatigue or exhaustion.

After exercise, when muscle pumping ceases, the blood can begin to pool rapidly in the legs or abdomen, while the rate of sympathetic noradrenergic nerve traffic falls to the resting rate. If the decline in nerve traffic did not balance the decline in production of byproducts of metabolism, then the blood pressure would fall after exercise. At the same time, loss of body fluid via evaporative sweating tends to decrease the blood volume. Patients with a dysautonomia therefore can feel bad not only during exercise but also after exercise. It is important to stay hydrated and to avoid activities like eating a large meal immediately after exercise, because this can divert already limited blood volume to the gut.

Perhaps surprisingly, even vigorously healthy, muscular, lean people can have a susceptibility to faint, and it is unclear if exercise training in general helps them. On the other hand, some patients can improve by isometric calf muscle training, where the patient learns to tense anti-gravity muscles. This tends to decrease the amount of pooling of blood in the legs. At the time of an acute episode, isometric counter-maneuvers such as leg crossing and tightening the buttocks can temporarily maintain consciousness.

PACEMAKERS AND SINUS NODE ABLATION

Whether insertion of a cardiac pacemaker helps patients with autonomically mediated syncope is controversial. Having a

pacemaker inserted may not be a cure, because the low pulse rate at the time of fainting might not cause the low blood flow to the brain that results in the loss of consciousness. On the other hand, a sudden absence of electrical activity in the heart (asystole) produces loss of consciousness within seconds, and in patients with chronic orthostatic intolerance and tilt-evoked asystole, a pacemaker could be curative.

Some patients who have a very fast pulse rate undergo destruction of the sinus node pacemaker cells in the heart (sinus node ablation). The doctor must be sure that the fast pulse rate

Class I (USEFUL)

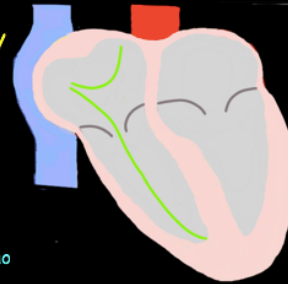
1. Recurrent syncope caused by carotid sinus stimulation; minimal carotid sinus pressure induces ventricular asystole of >3 seconds' duration in the absence of any medication that depresses the sinus node or AV conduction.

Class IIa (CONFLICTING EVIDENCE, WEIGHT IN FAVOR OF EFFICACY)

1. Recurrent syncope without clear, provocative events and with a hypersensitive cardioinhibitory response.
2. Syncope of unexplained origin when major abnormalities of sinus node function or AV conduction are discovered or provoked in electrophysiological studies.

Class IIb (CONFLICTING EVIDENCE, USEFULNESS LESS WELL ESTABLISHED BY EVIDENCE OR OPINION)

1. Neurally mediated syncope with significant bradycardia reproduced by a head-up tilt with or without isoproterenol or other provocative maneuvers.



According to ACC/AHA Practice Guidelines, cardiac pacemaking is useful for recurrent syncope associated with ventricular asystole lasting >3 seconds caused by carotid sinus stimulation.

results from a problem with the heart and does not result from a compensation by the sympathetic noradrenergic system for another problem, such as low blood volume, because

eliminating the compensation could make the patient worse rather than better. Sinus node ablation is not thought to help patients with POTS.

NEUROSURGERY

Some patients with chronic orthostatic intolerance have a type of change in the brainstem called Chiari malformation. This is an anatomic abnormality where part of the brainstem extends below the hole in the skull between the brain and spinal cord. Neurosurgery can correct the malformation, but the orthostatic intolerance does not necessarily disappear. This is a controversial topic, and patients should seek a second opinion before agreeing to this procedure.

CONSTIPATION OR URINARY RETENTION

Patients with failure of the parasympathetic nervous system (PNS) can have problems with constipation and retention of urine in the bladder. Low PNS activity could be the result of abnormal brainstem reflexes rather than PNS deficiency itself. The constipation is treated non-specifically, with stool softeners, bulk laxatives, milk of magnesia, magnesium citrate, senna, or cascara.

Urinary retention can be associated with urinary incontinence and is a common finding in multiple system atrophy. Drugs that stimulate receptors for acetylcholine, such as urecholine, might be tried. Often patients with autonomic failure must learn to self-catheterize to empty the bladder, by inserting a plastic or rubber tube into the urethra and then into the bladder,

in order to obtain relief.

Drug Treatments

Several drugs are used to treat dysautonomias. Some of them are powerful or can produce harmful side effects. Patients should take medications only under the supervision of a doctor with expertise and experience in the treatment of dysautonomias.

Different centers use different drugs from a long “menu” to treat dysautonomias.

The following is a summary of some of the drugs used to treat dysautonomias.

Drug	Goal of Treatment
Fludrocortisone (=Florinef™)	Increase blood volume Increase blood pressure
Midodrine (=Proamatine™)	Tighten blood vessels Increase blood pressure Prevent fainting
Beta-Blocker	Decrease heart rate Decrease blood pressure Decrease adrenaline effects Prevent fainting
Erythropoietin (=Procrit™)	Increase blood count Increase blood pressure
Amphetamines	Tighten blood vessels Increase alertness

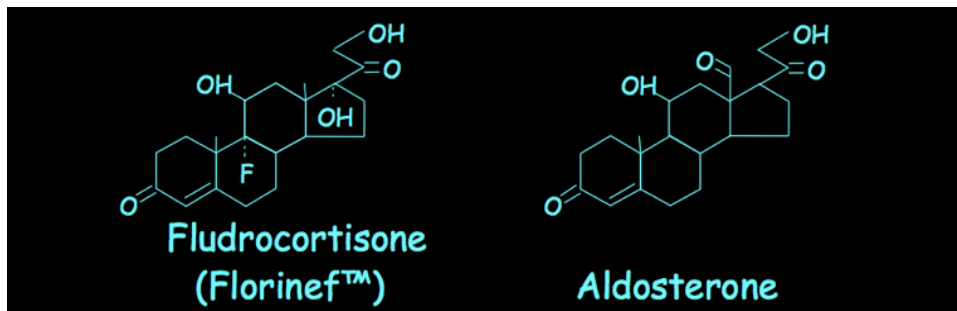
Desmopressin (=DDAVP™)	Tighten blood vessels
“NSAID”	Tighten blood vessels
Somatostatin (=Octreotide™)	Tighten blood vessels in gut
Selective Serotonin Reuptake Inhibitor (=SSRI)	Improve mood, allay anxiety
“Tricyclic”	Improve mood
Alprazolam (=Xanax™)	Increase sense of calmness Improve sleep
Clonidine (=Catapres™)	Decrease blood pressure Improve sleep
Bethanechol (=Urecholine™)	Increase salivation Improve gut action Improve urination
Yohimbine	Increase blood pressure
Pyridostigmine (=Mestinon™)	Increase blood pressure
L-DOPS (=Droxidopa, Northera™)	Increase blood pressure

FLUDROCORTISONE (FLORINEF™)

Fludrocortisone (Florinef™) is a man-made type of drug called a salt-retaining steroid, or mineralocorticoid. The drug closely resembles the body’s main salt-retaining steroid, aldosterone.

Florinef must be taken with a high-salt diet in order for the drug to work. Florinef forces the kidneys to retain sodium in exchange for potassium. Water follows the sodium, and so Florinef is thought to increase the blood volume. The patient

gains “fluid weight,” and blood pressure increases. Because of the tendency of Florinef to waste potassium, Florinef can cause a fall in the serum potassium level, which if severe can be dangerous. Patients taking Florinef should have periodic checks of their serum potassium level, and if it is low they should take a potassium supplement.



Fludrocortisone closely resembles aldosterone, the main salt-retaining steroid of the body.

Fludrocortisone (Florinef™) forces the body to retain salt.

Florinef™ treatment increases the blood pressure regardless of the patient's posture. The increased blood pressure when the patient is standing may be large enough that the patient does not have lightheadedness or other symptoms of orthostatic intolerance.

Florinef™ given to patients with chronic autonomic failure can cause or worsen high blood pressure when the patient is lying down. Sometimes the doctor faces a difficult dilemma—balancing the long-term increased risk of stroke, heart failure, or kidney failure from high blood pressure against the immediate risk of fainting or falling from orthostatic

hypotension.

In some patients with chronic orthostatic intolerance such as POTS, Florinef™ can produce improvement; however, in other patients there is no improvement. Perhaps treatment with a salt-retaining steroid is effective only in POTS patients who have low blood volume or decreased ability of the kidneys to reabsorb filtered sodium.

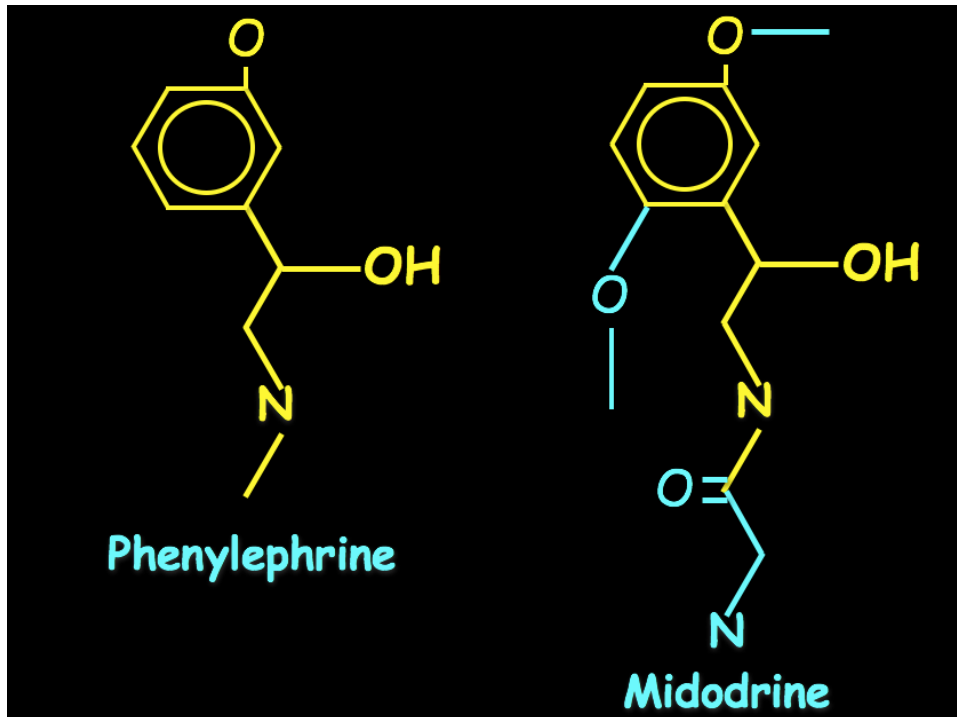
MIDODRINE

Midodrine (Proamatine™) tightens blood vessels throughout the body. That is, midodrine is a vasoconstrictor. The drug works by stimulating alpha- adrenoceptors in blood vessel walls. When a person stands up, the sympathetic noradrenergic system is activated reflexively, the chemical messenger norepinephrine is released from the sympathetic nerves in blood vessel walls, the norepinephrine binds to alpha-adrenoceptors in the blood vessel walls, and the stimulation of the alpha-adrenoceptors causes the blood vessels to constrict (vasoconstriction), increasing the blood pressure.

Midodrine works like artificial norepinephrine, increasing blood pressure (BP).

In patients with orthostatic hypotension related to a loss of sympathetic noradrenergic nerves, there is little norepinephrine to release. In this situation, the blood vessels become supersensitive (denervation supersensitivity), perhaps by the alpha-adrenoceptors accumulating on the surface of the cells in blood vessel walls. In patients with “denervation

supersensitivity” midodrine can be very effective in raising the blood pressure.



Midodrine, which resembles phenylephrine structurally, works like artificial norepinephrine, increasing blood pressure (BP) by stimulating alpha-adrenoceptors in blood vessel walls.

In using midodrine to treat elderly men with orthostatic hypotension, the doctor should be aware that stimulation of alpha-adrenoceptors can worsen symptoms of prostate problems, such as urinary retention, urgency, and decreased urinary stream.

Alpha-1 adrenoceptor blockers are effective in treating benign prostatic hypertrophy (BPH), and alpha-1 adrenoceptors blockers interfere with midodrine’s effects.

In patients with neurogenic orthostatic hypotension, the symptoms are often worst in the morning. As the day goes on, the blood pressure increases. One may not need an alpha-adrenoceptor agonist throughout the day, and in patients with sympathetic denervation taking midodrine around the clock might desensitize the alpha-adrenoceptors. It is reasonable to try taking midodrine early in the morning before getting up and then perhaps at lunchtime to avoid post-prandial hypotension but not to take it later in the day, so that by the next morning the drug has worn off and the alpha-adrenoceptors are super-sensitive again.

BETA-ADRENOCEPTOR BLOCKERS

Beta-adrenoceptor blockers interfere with some effects of norepinephrine and adrenaline. Norepinephrine and adrenaline produce their effects by binding to specific receptors on the target cells, such as heart muscle cells. Beta-blockers interfere with this binding.

There are two types of receptors for norepinephrine and adrenaline, called alpha-adrenoceptors and beta-adrenoceptors. Adrenaline stimulates both types. Adrenaline tightens blood vessels in most parts of the body, such as the skin, due to stimulation of alpha-adrenoceptors in blood vessel walls. Vasoconstriction of skin blood vessels decreases local blood flow, and the skin becomes pale. This is why pallor can be a sign of high adrenaline levels. In skeletal muscle, however, adrenaline generally relaxes blood vessels, due to stimulation of beta-2 adrenoceptors. By this action adrenaline tends to shunt

blood toward skeletal muscle. This makes sense in terms of the need for abundant blood flow to skeletal muscle in emergency situations. Adrenaline also stimulates beta-adrenoceptors in the heart, and this increases the force and the rate of the heartbeat. Because of the effects on the heart, the amount of blood pumped by the heart per minute (cardiac output) increases.

Beta-1 adrenoceptors and beta-2 adrenoceptors are abundant in the human heart; stimulation of these receptors produces about the same effects.

All beta-blockers decrease the rate and force of the heartbeat.

On skeletal muscle blood vessels and in the lungs, beta-2 adrenoceptors are much more abundant than are beta-1 adrenoceptors. Stimulation of beta-2 adrenoceptors on smooth muscle cells of the airways relaxes the airways. This is a reason that beta-2 adrenoceptor stimulants are used to treat asthma.

Drugs that act at beta-adrenoceptors are often grouped in terms of whether they are “selective” for beta-1 adrenoceptors or are “non-selective,” meaning they block the other types of beta-adrenoceptors as well. There are no approved drugs that block beta-2 adrenoceptors selectively.

In patients with autonomically mediated syncope and high levels of adrenaline in the bloodstream, the adrenaline stimulates beta-2 adrenoceptors on blood vessels in skeletal muscle. This relaxes the blood vessels and decreases the

resistance to blood flow. Blood may then be shunted away from the brain and towards the skeletal muscle, contributing to lightheadedness or loss of consciousness. In such patients, non-selective beta-adrenoceptor blockers might be preferable to selective blockers.

Beta-adrenoceptor blockers decrease the pulse rate, the force of heart contraction, and the systolic blood pressure. In patients with rapid pulse rates, associated with a sense of pounding or irregular beating of the heart (palpitations) or chest pain, beta-adrenoceptor blockers decrease the heart rate and can help relieve the pain and prevent abnormal heartbeats or heart rhythms. These drugs are also commonly used to treat long-term high blood pressure (hypertension). Because of decreased systolic blood pressure and heart rate, the rate of consumption of oxygen by the heart decreases, and this can help patients with coronary artery disease.

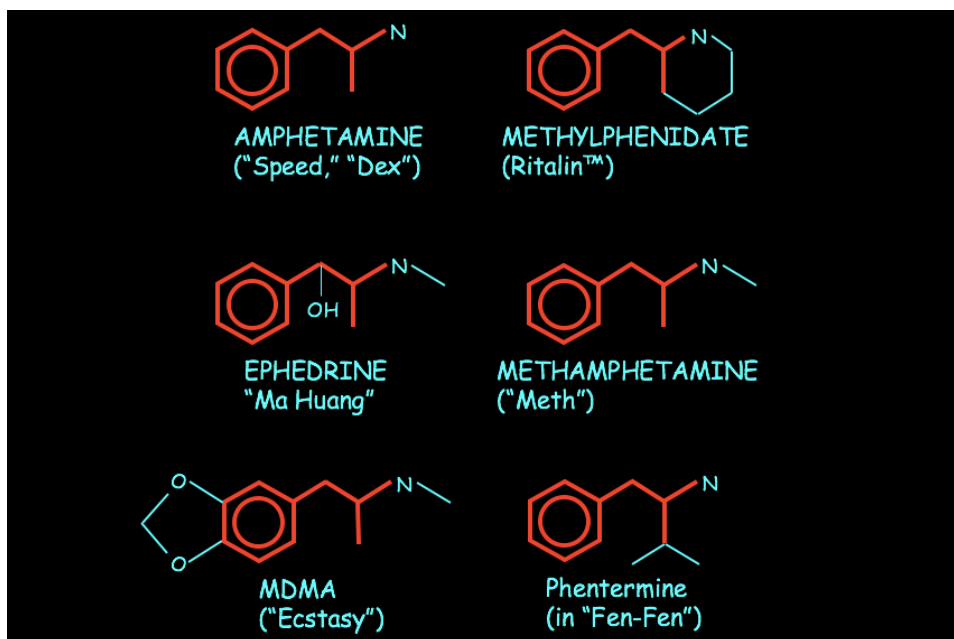
In postural tachycardia syndrome (POTS) the value of treatment with beta-adrenoceptor blockers may depend on whether the rapid pulse rate when the patient stands up reflects a primary or compensatory response. If the rapid pulse rate were a compensation for another problem, such as low blood volume due to menstrual bleeding, then blocking that compensation would not help the patient. But if the rapid pulse rate were the result of an inappropriate, excessive rate of sympathetic nerve traffic to the heart, or there were a high intrinsic heart rate, then a beta-adrenoceptor blocker could help the patient.

AMPHETAMINES

Amphetamines are chemicals that resemble the drug, dextro-amphetamine (d-amphetamine).

Amphetamines are in a class of drugs called indirectly acting sympathomimetic amines. They produce their effects at least partly by increasing delivery of norepinephrine to its receptors, both in the brain and outside the brain.

By way of effects in the brain, amphetamines increase the state of arousal and attention, prevent or reverse fatigue, decrease appetite, and at high doses increase the rate and depth of breathing. They also increase blood pressure, probably by multiple mechanisms in the brain and periphery.



Amphetamines share a particular chemical structure (alpha-methyl-phenylethylamine).

Pseudoephedrine (Sudafed™) is structurally a mirror image (stereoisomer) of ephedrine. This difference changes the properties of the drug, producing much less central nervous system stimulation. By releasing norepinephrine from sympathetic nerve terminals in the mucous membranes of the nasal airways, pseudoephedrine tightens blood vessels, making them less leaky and thereby relieving nasal congestion.

In a laboratory pseudoephedrine can be converted easily to other amphetamines that are abused drugs. This is why over-the-counter sales of pseudoephedrine are now restricted.

Methylphenidate (Ritalin™), another sympathomimetic amine, is used commonly to treat attention deficit-hyperactivity disorder.

Amphetamines work both inside and outside the brain. They increase attention, decrease appetite, interfere with sleep, and often increase the blood pressure.

Phenylpropanolamine (PPE) was used in over-the-counter diet pills until the discovery of serious adverse effects such as severe high blood pressure and stroke. PPE was taken off the non-prescription drug market.

Phentermine prescribed with fenfluramine (“Phen-Fen”) was an effective combination to decrease weight, until serious adverse effects of this combination came to light, and this combination is no longer prescribed.

In treating patients with dysautonomias, amphetamines should

be used sparingly because of the potential for tolerance and dependence. In patients with sympathetic neurocirculatory failure from abnormal regulation of sympathetic nerve traffic to intact sympathetic nerves, this type of drug releases norepinephrine from the terminals and increases the blood pressure. Some patients with chronic orthostatic intolerance can improve.

INTRAVENOUS SALINE INFUSION

Inability to tolerate prolonged standing can result from low blood volume, excessive pooling of blood in the veins of the legs, pelvis, or abdomen during standing, or exit of fluid from the blood vessels into the tissues (extravasation).

In these situations, IV infusion of physiological saline solution can temporarily improve the ability to tolerate standing up.

Saline infusion temporarily increases the blood volume.

IV saline infusion can also be useful for diagnostic purposes. Some patients with chronic orthostatic intolerance benefit from

IV saline infusion given a few times per week by way of a permanent intravenous catheter. The clinician must weigh the potential benefit against the not insubstantial risks, such as of infection and intravascular clotting.

DESMOPRESSIN (DDAVP™)

Desmopressin (DDAVP™) is a synthetic drug used as replacement for the hormone, vasopressin. Vasopressin tightens blood vessels and raises the blood pressure. Vasopressin is also called anti-diuretic hormone (ADH), because it causes the kidneys to retain water and therefore decreases production of urine. Desmopressin taken nasally is occasionally used to treat orthostatic hypotension in patients with chronic autonomic failure.

SOMATOSTATIN (OCTREOTIDE™)

Somatostatin (Octreotide™) is a hormone that inhibits the release of another hormone, growth hormone, from the pituitary gland at the base of the brain. Somatostatin can tighten blood vessels, especially in the gastrointestinal tract, and raise the blood pressure of patients with orthostatic hypotension. The drug must be injected, and it is expensive.

PYRIDOSTIGMINE (MESTINON™)

Pyridostigmine (Mestinon™) is a drug that works by blocking the enzyme that breaks down acetylcholine. Acetylcholine is the chemical messenger that is responsible for transmission of autonomic nerve impulses in ganglia. By inhibiting breakdown of acetylcholine, pyridostigmine is thought to increase activity of the sympathetic nervous system and improve orthostatic hypotension in patients with chronic autonomic failure.

Because pyridostigmine also increases activity of the

parasympathetic nervous system, the drug can increase salivation and stimulate gastrointestinal or urinary bladder contractions. There may be psychological changes because of actions of the drug in the brain. By increasing activity of the sympathetic cholinergic system pyridostigmine can increase sweat production. The drug may also increase adrenaline release.

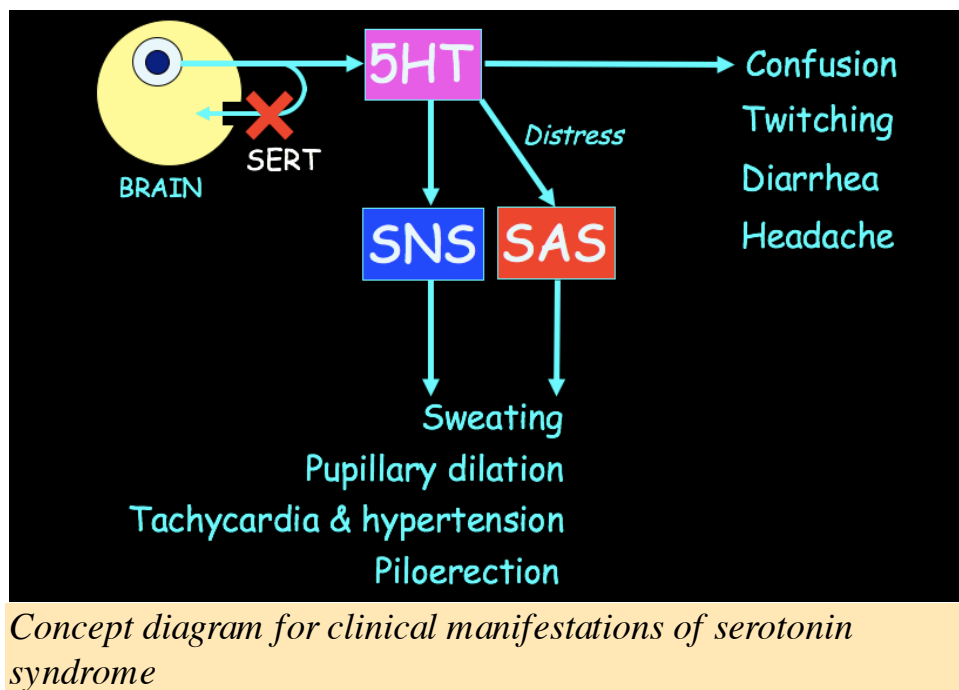
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)

SSRIs inhibit a key process that is required for inactivating and recycling the chemical messenger, serotonin. The process is reuptake of released serotonin back into the nerve terminals that store it. SSRIs are widely used to treat depression, anxiety, and other psychiatric or emotional problems. They are also used to treat some forms of dysautonomias.

Serotonin Syndrome

Drugs that directly or indirectly increase occupation of serotonin receptors can produce a syndrome of confusion, twitching, diarrhea, headache, and evidence of sympathetic activation.

Another word of caution is in order in the treatment of teen-aged dysautonomia patients who are depressed: Monoamine reuptake blockers have been statistically associated with an increased risk of suicide.



CLONIDINE (CATAPRES™)

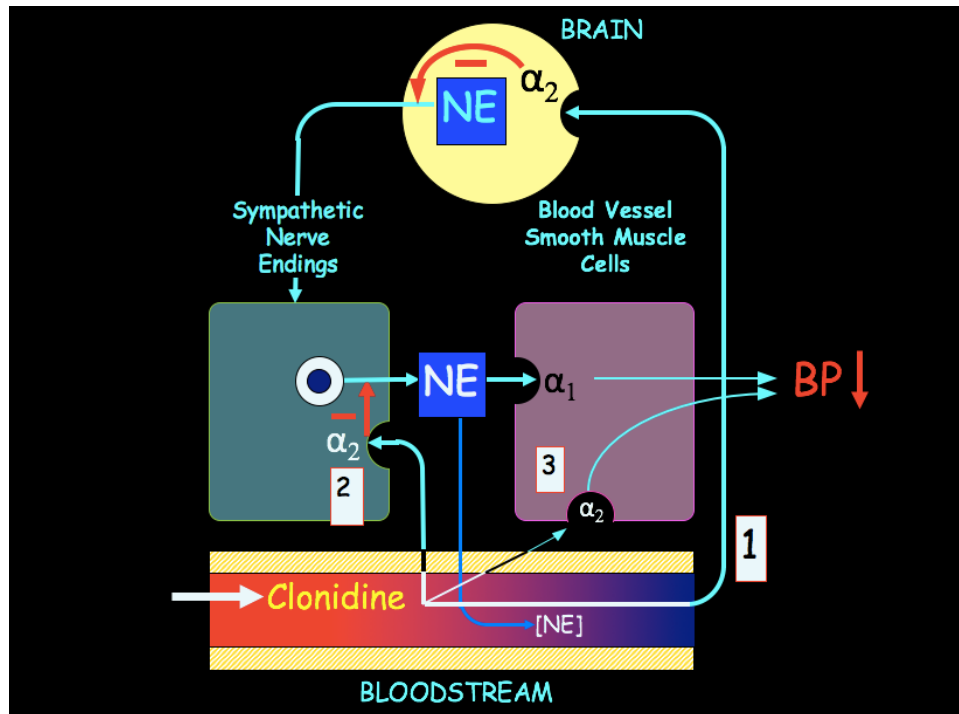
There are two types of alpha-adrenoceptors, called alpha-1 and alpha-2. Stimulation of either type of receptor in blood vessel walls causes the vessels to constrict (vasoconstriction).

Clonidine stimulates alpha-2 adrenoceptors. Stimulation of alpha-2 adrenoceptors in the brain decreases the rate of sympathetic nerve traffic. Stimulation of alpha-2 adrenoceptors on sympathetic nerves decreases the amount of release of the chemical messenger, norepinephrine, from the nerves. Even though clonidine stimulates a type of alpha- adrenoceptor, clonidine normally decreases the blood pressure.

Clonidine works both in the brain and outside the brain. It

decreases the blood pressure and often causes drowsiness.

There are several uses of clonidine in the diagnosis and treatment of dysautonomias. In the clonidine suppression test, clonidine is used to separate high blood pressure due to increased sympathetic nervous system activity from high blood pressure due to a tumor that produces catecholamines—pheochromocytoma.



Clonidine decreases sympathetic noradrenergic outflows and decreases norepinephrine release for a given amount of sympathetic nerve traffic.

Clonidine works both in the brain and outside the brain. It decreases the blood pressure and often causes drowsiness.

In patients with long-term high blood pressure (hypertension) due to excessive release of norepinephrine from sympathetic nerves (hypernoradrenergic hypertension), clonidine can be very effective in lowering the blood pressure. Clonidine is also effective in treating withdrawal from some addictive drugs.

Clonidine often causes drowsiness and dry mouth. The sedation often limits its clinical use.

ERYTHROPOIETIN (PROCRIT™)

Procrit™ (Erythropoietin) is a particular hormone that is used as a drug. Erythropoietin in the body is released into the bloodstream by the kidneys and acts on the bone marrow to increase the production of red blood cells. Procrit™ is helpful to treat low red blood cell counts (anemia), such as in kidney failure. Anemic patients look pale and feel tired.

By mechanisms that remain incompletely understood, Procrit™ tends to increase the blood pressure. Some doctors prescribe Procrit™ to treat low blood pressure in patients with chronic fatigue syndrome who have a low red blood cell count.

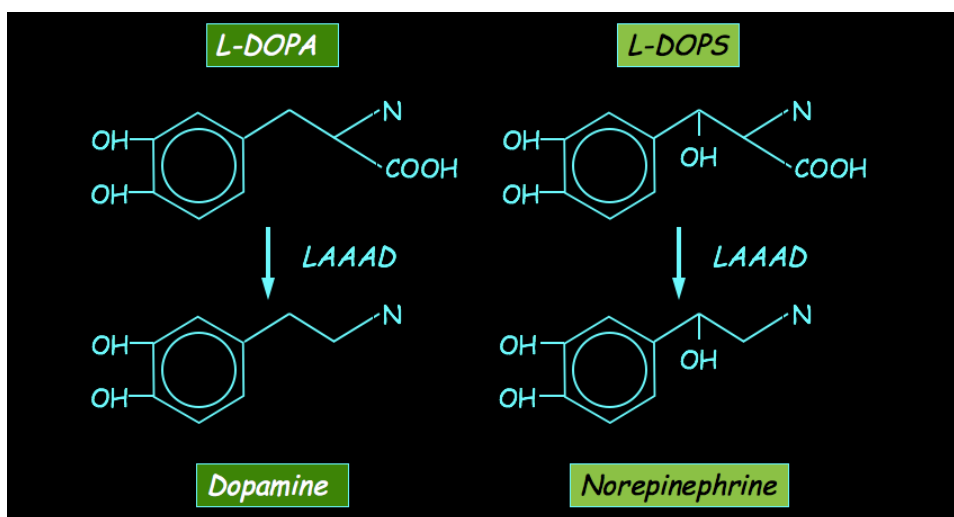
L-DOPS (NORTHERA™)

L-Dihydroxyphenylserine (L-DOPS, droxidopa, Northera™) is a type of chemical called an amino acid. It is very closely related chemically to L-dihydroxyphenylalanine (Levodopa, L-DOPA), which is an effective drug to treat Parkinson's disease. L-DOPA works by being converted in the brain to the catecholamine, dopamine. L-DOPS works by being converted

to the closely related catecholamine, norepinephrine, mainly outside the brain.

L-DOPS is converted to norepinephrine, like L-DOPA is converted to dopamine.

L-DOPS is a neutral amino acid and as such it is taken up into all cells via the neutral amino acid transporter. In cells of the



As L-DOPA is converted to dopamine by L-aromatic-amino-acid decarboxylase (LAAAD), so is L-DOPS converted to norepinephrine.

gut, liver, kidneys, and other organs that contain abundant L-aromatic-amino-acid decarboxylase (LAAAD), L-DOPS is converted to norepinephrine (NE). This means that L-DOPS can provide NE even in the absence of sympathetic nerves.

Because L-DOPS is a norepinephrine pro-drug, L-DOPS administration leads indirectly to stimulation of alpha-

adrenoceptors in blood vessel walls, causing the vessels to constrict and increasing the blood pressure.

L-DOPS was recently approved by the US FDA for symptoms of orthostatic hypotension.

A potential problem with using L-DOPS to treat orthostatic hypotension in patients with Parkinson's disease is that the patients often are treated at the same time with Sinemet™. Sinemet™ is a combination of L-DOPA and carbidopa. The carbidopa interferes with the conversion of L-DOPA to dopamine. Since carbidopa does not enter the brain, the combination results in increased delivery of DOPA to the brain and increased production of dopamine. Carbidopa also interferes with the conversion of L-DOPS to norepinephrine. This might blunt the hoped-for increase in blood pressure by L-DOPS treatment; however, it appears that the dose of carbidopa in Sinemet™ is too small to prevent the increase in blood pressure.

YOHIMBINE

When alpha-2 adrenoceptors in the brain are blocked, this increases sympathetic nerve traffic and increases the amount of norepinephrine release for a given amount of sympathetic nerve traffic.

Yohimbine works both in the brain and outside the brain. The drug increases blood pressure and the state of alertness.

Yohimbine blocks alpha-2 adrenoceptors in the brain and on sympathetic nerve terminals, and so it releases norepinephrine from the terminals. The released norepinephrine binds to alpha-1 adrenoceptors in blood vessel walls. This causes the blood pressure to increase.

Even though yohimbine blocks alpha-2 adrenoceptors in blood vessel walls, the drug releases so much norepinephrine, and there are so many alpha-1 adrenoceptors in blood vessel walls, that normally yohimbine increases the plasma norepinephrine level and increases the blood pressure.

In patients with chronic autonomic failure and an inability to regulate sympathetic nerve traffic in intact nerves, such as in the MSA, yohimbine releases norepinephrine from the terminals and effectively increases the blood pressure. Theoretically, in patients with autonomically mediated syncope or POTS, yohimbine might attenuate sympathoadrenal imbalance and thereby prevent fainting episodes.

Yohimbine can cause trembling, paleness of the skin, goose bumps, hair standing out, an increase in salivation, or emotional changes.

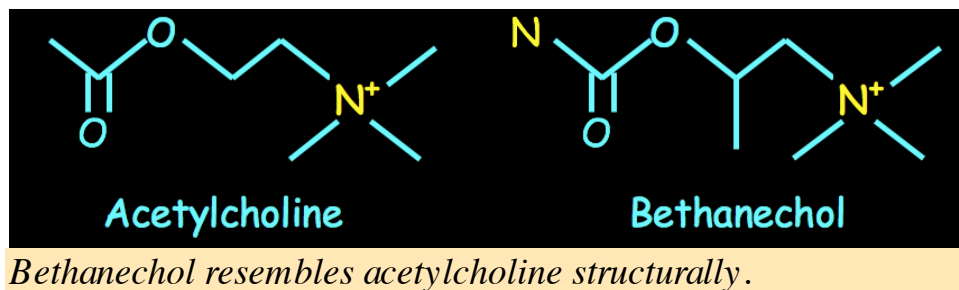
Oral yohimbine was approved as a prescription drug to treat impotence from erectile dysfunction in men, but the drug is no longer marketed. Yohimbine in the form of yohimbe bark can be purchased in health food stores.

BETHANECHOL (URECHOLINE™)

Bethanechol is a drug that stimulates receptors for acetylcholine, the chemical messenger in autonomic ganglia and the parasympathetic nervous system. The drug increases production of saliva, increases gut activity, and increases urinary bladder tone.

Bethanechol increases the muscle tone of the bladder, digestive motions of the gut, and salivation. It might be useful to treat urinary retention or constipation in patients with chronic autonomic failure.

Although bethanechol resembles acetylcholine structurally, bethanechol is not broken down by acetylcholinesterase.



Urecholine™ increases production of saliva, increases gut activity, and increases urinary bladder tone.

METOCLOPRAMIDE

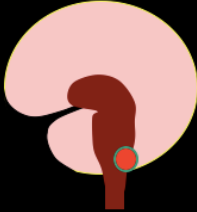
Metoclopramide is a medication used to alleviate nausea and vomiting and to treat symptoms of gastroparesis and

gastroesophageal reflux disease (GERD).

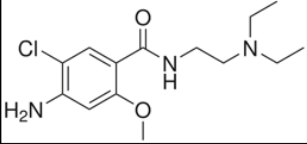
The drug acts as an antagonist of dopamine D₂ receptors. As such, it can worsen parkinsonism or evoke tardive dyskinesia. Tardive dyskinesia is a rare but serious complication of dopamine receptor antagonists in which the patient has involuntary movements of the jaw or tongue. Tardive dyskinesia can persist even after the drug is withdrawn.

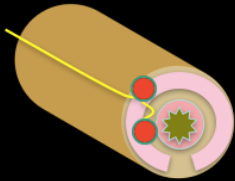
METOCLOPRAMIDE

Dopamine D₂ receptor antagonist
(& mixed 5-HT₃ receptor antagonist/5-HT₄ agonist)



Anti-nausea
(but risk of parkinsonism,
dyskinesias, tardive dyskinesia,
akathisia, neuroleptic malignant
syndrome, depression, SVT,
galactorrhea)

CCN(CC)CCNC(=O)c1cc(N)cc(OC)c1Cl



Improves symptoms of gastroparesis, GERD
(but risk of constipation/diarrhea)

Uses and side effects of metoclopramide

Metoclopramide also can produce other dyskinesias, possibly via inhibiting D₂ receptors on dopaminergic terminals and augmenting dopamine release.

MANAGING POTS OR AUTONOMICALLY MEDIATED SYNCOPE

An early step in management of chronic orthostatic intolerance is to search carefully for common, reversible causes, such as diabetes, weight loss, prolonged bed rest, debilitating diseases, and medications.

In devising an individual treatment plan, it may be worthwhile to consider whether the POTS results from low blood volume, decreased tone of blood vessels, a primary form of hyperactivity of the sympathetic noradrenergic system, or physical de-conditioning. If there were low blood volume, then treatment with water, salt, fludrocortisone, or IV saline would be rational. If there were decreased tone of arterioles, then midodrine, a sympathomimetic amine, or L-DOPS would make sense, while if there were decreased tone of veins then compression hose or an abdominal binder could work. If there were a primary increase in sympathetic noradrenergic system outflow to the heart, then a beta-blocker would be in order. Finally, because of the debility caused by POTS, patients can get into a vicious cycle of bed rest, decreased cardiovascular and skeletal muscle tone, worse exercise intolerance and fatigue, and more bed rest. Enrolling in an individualized exercise conditioning program can be very beneficial.

Treatment of POTS should be tailored to the individual patient.

Drug treatments for POTS generally have attempted to increase

blood volume, such as using Florinef™ and liberal salt and water intake, injections of erythropoietin, or IV infusions of saline; block fast pulse rates, such as using β -adrenoceptor blocker; decrease exaggerated norepinephrine release, such as using clonidine; or enhance vasoconstriction, such as using midodrine or octreotide. Non-drug treatments include abdominal compression (e.g., a doubled bicycle leotard or abdominal binder), venous compression hose, anti-gravity muscle resistance training, exercise training, or even insertion of a pacemaker.

Often these treatments, while helpful, do not bring the patients back to a sense of normal health. Over the course of months or years, the patients can improve, or else they learn to cope with this chronic, debilitating, but not life-threatening disorder.

If orthostatic tachycardia were primary, then treating it would help the patient, but if it were secondary, then treating the tachycardia would not help the patient. Keeping this in mind may help understand how one patient can feel better from treatment with a beta-blocker, which forces the pulse rate to go down, while another may not feel better at all, even though the pulse rate has decreased to the same extent.

Treatments for autonomically mediated syncope are about the same as for POTS: Florinef™ and liberal salt and water intake, β -adrenoceptor blockers, midodrine, anti-gravity muscle resistance training, or exercise training. In patients with syncope that is associated with actual cessation of the heartbeat (asystole), insertion of a pacemaker may be indicated. Consistent with the notion that decreased sympathetic nerve traffic or decreased norepinephrine release predisposes to

neurocardiogenic syncope, some patients note improvement with sympathomimetic amines such as d-amphetamine or methylphenidate (Ritalin™).

Theoretically, a benzodiazepine to inhibit adrenaline release in distressing situations could prevent sympathoadrenal imbalance; however, this hypothesis has not been tested.

MANAGING HYPERHIDROSIS

Hyperhidrosis is excessive sweating, usually in the hands, armpits, or face. This condition involves an abnormality of the sympathetic cholinergic system, which is the main component of the autonomic nervous system involved with sweating. Idiopathic hyperhidrosis has no known cause and can occur without evidence of functional abnormalities of other components of the autonomic nervous system.

Treatments used for hyperhidrosis include anti-perspirants, botulinum toxin, gabapentin, anti-cholinergics, and endoscopic thoracic sympathectomy (ETS).

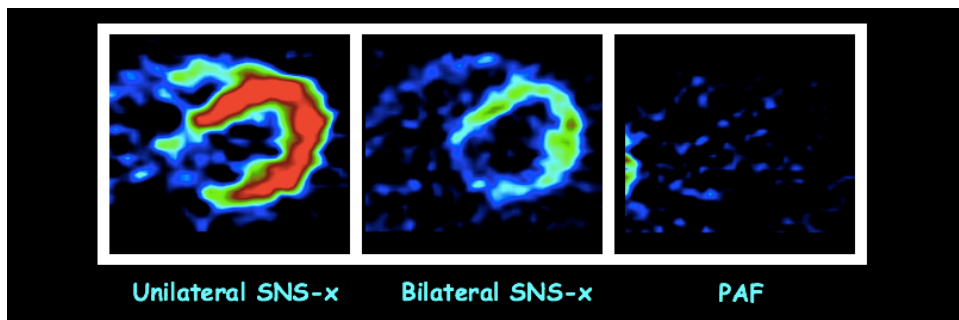
Glycopyrrolate, a muscarinic cholinergic antagonist, can be taken as a liquid or applied locally as a cream. Given systemically, glycopyrrolate can produce several side effects such as dry mouth and constipation. Unfortunately, there is no commercial source of glycopyrrolate cream for topical use; this form of the drug can be produced by a compounding pharmacy. Applied locally with an occlusive dressing, the drug is absorbed through the skin quite slowly, so that decreasing sweating may take several hours.

ETS is done at several centers worldwide. There has been aggressive marketing of the procedure as a safe cure; however, there can be long-term side effects. These include compensatory hyperhidrosis below the level of the surgery (in the abdomen, back, groin, or feet).



Compensatory hyperhidrosis below the level of the surgery can be a long-term side effect of endoscopic thoracic sympathectomy (ETS).

After ETS some people (an unknown percentage) experience a “post-ETS” syndrome of decreased exercise tolerance, insomnia, decreased heart rate responsiveness, and apathy. One may speculate that these non-specific symptoms are related to effects of partial cardiac denervation.



Partial cardiac sympathetic denervation revealed by ^{18}F -dopamine scanning in a patient who had undergone bilateral endoscopic thoracic sympathectomies.

Living with Dysautonomias

This section, on living with dysautonomias, is focused on the patient, you.

Living successfully with a dysautonomia requires understanding about how the body's "automatic nervous system" (autonomic nervous system) functions and how changes in autonomic nervous system function cause symptoms. The first part of this book covers these topics.

Living successfully with a dysautonomia also requires understanding how chronic illness impacts patients, caregivers, and families—at home, at school, and at work. The changes you and your family may face can impose new emotional burdens. Coping with a form of dysautonomia almost certainly necessitates important changes in lifestyle. This section offers practical guidance for living successfully with dysautonomias.

FINDING AND WORKING WITH A PHYSICIAN

Because there are many different types of dysautonomias, and because disease mechanisms in dysautonomias often are not well understood in individual patients, your doctor and you will likely spend a lot of time trying to find reversible causes and devising a treatment program. For these reasons the relationship between your physician and you is crucial.

Despite the fact that dysautonomias affect over a million

Americans, you will probably find that very few people and surprisingly few doctors have ever heard of dysautonomias. It may be that no doctors in your area specialize in treating autonomic disorders.

Few doctors have heard of dysautonomias.

Research over the last few years has increased awareness of the large number of people who are affected by dysautonomias. Dr. David Robertson, of the Autonomic Dysfunction Center at Vanderbilt University, has called this awakening an “epidemic of disease recognition.” With growing awareness, these disorders should become easier to recognize and treat.

The medical terminology can be confusing even to doctors. The same basic set of symptoms and signs can be called by a variety of names. For example, symptoms of a long-term inability to tolerate standing up—chronic orthostatic intolerance—have been labeled as “POTS” (Postural Orthostatic Tachycardia Syndrome, or postural tachycardia syndrome), “COI” (chronic orthostatic intolerance), Mitral Valve Prolapse-Dysautonomia Syndrome, Neurocirculatory Asthenia, Soldier’s Heart, neurally mediated hypotension, and other names in a long list. No wonder many patients feel frustrated and confused!

Finding a physician able to diagnose, treat, and follow patients with dysautonomias will likely take effort on your part. Unlike diseases or conditions that affect only one part of the body, dysautonomias can affect virtually every organ and system. Components of the autonomic nervous system play a variety of

roles in regulating many largely automatic, involuntary, unconscious functions, such as breathing, blood pressure, heart rate, digestion, and urination. Because of the multi-dimensional aspects of dysautonomias, it is often difficult to determine which type of physician should manage the condition.

Your care will likely also require extra effort by your doctor. Since the cause of your symptoms may not be well understood, developing an effective treatment plan is likely to take time. People with dysautonomias must be both patient and persistent. Because of large differences among patients, and continuing mystery about mechanisms of dysautonomias, doctors need to learn from their patients about what works and what doesn't.

Your first priority should be to find a physician willing to work with you. Whether that physician is a cardiologist, neurologist, endocrinologist, psychiatrist, internist, or family practitioner is less important than his or her ability to work with you and other physicians on your behalf.

Find a doctor who will work with and learn from you.

Because little is known about underlying mechanisms of many forms of dysautonomia, the physician will probably focus on treating symptoms without really knowing their exact cause. For this reason, much of what is done is through trial and error. Both you and your physician will need to understand that finding a program that works requires time, patience, and open and honest communication. Your relationship and ability to communicate with your doctor will make a big difference in putting together an effective therapy program.

Your symptoms are likely to change over time. Keep your doctor informed about how you are doing and about changes you notice. For instance, a particular medication might make you feel better in one way but worse in another. Your doctor might be able to change your prescription or start you on another drug that would work the same way but with fewer side effects. If you notice major improvements, you should inform your doctor. It's possible you may not need as much medication to manage the problem.

Keep your doctor informed.

You should develop a plan with your doctor about symptoms that require immediate attention and those that can wait for a return visit. A brief discussion about this will help give you peace of mind when your symptoms are of concern.

Talking with a physician about multiple symptoms can be a problem, if you've had unpleasant interactions at office visits in the past. You might be concerned about what your doctors might think: "What if they think I'm CRAZY?" Don't let this concern keep you from relaying everything the doctor needs to know. You can't expect your physician to put the puzzle together if you withhold half the pieces. Tell your physician about all your symptoms. Let your doctor decide what is important information.

Create a bullet list of questions to ask. Keep in mind that your doctor has limited time to discuss your condition and treatment. Before visiting your doctor, ask yourself, "If I could improve one symptom, which would it be?" This type of thought

process will give you and your physician a better opportunity to work on the symptoms that cause you the most trouble.

You may want to consider having a family member or friend go with you. Having someone with you may make you feel more comfortable, and a family member or friend can also give your physician details you may not recall.

Keeping a daily journal can also be a useful tool, both for you and your doctor. This may allow your doctor an opportunity to diagnose your condition and see trends or patterns in your symptoms. You might include blood pressure, pulse rate, body weight, and the timing and circumstances of events that trigger symptoms, mood, activity, external temperature, time of day, time of the month, fluid intake—even thoughts. Talk to your doctor about which information to record. Let your doctor review your journal, since what may seem insignificant to you may be significant to your doctor. It is part of the nature of dysautonomias that symptoms often have peaks and valleys, and patients have good days and bad days.

If your doctor starts you on a new medication, it is important to discuss potential side effects. It is helpful to identify which symptoms are triggered as side effects of drugs and not as a result of your condition.

DAY BY DAY WITH DYSAUTONOMIA

Chronic Illness

Dysautonomias usually are chronic. They can continue for long

periods or even indefinitely. Many factors affect their courses, including heredity, environment, drug and non-drug treatments, and lifestyle. Living with a chronic illness poses continual challenges, marked by many ups, downs, and unexpected turns.

Living with a dysautonomia poses continual challenges.

Accepting Your Disorder

With an acute illness, you know you will eventually feel normal again. When you have a chronic illness, there is no cure in the traditional sense. You may never return to your “normal” way of life. Adaptation and acceptance therefore become important in maintaining your quality of life.

The first step to accepting your condition is to understand it. Knowing the “details” (e.g., common symptoms) can alleviate uncertainty and help you learn how to manage life with a dysautonomia.

Understand your condition.

Modifying Your Life

In the past you might have been able to work 8 hours and then do chores at home. Now doing so might put you in bed for a week! You may have to learn to pace your activities, take “baby steps.”

Coping successfully with a chronic illness requires significant lifestyle changes. Modifying your lifestyle to help you maintain as “normal” a life as possible can help you gain a sense of control over your illness, rather than feeling your illness controls you.

Making a weekly chart of activities/tasks can help. You might believe that you are not doing anything, yet when you review a list of your actual activities you might find you are trying to accomplish a great deal. The list can help you set priorities about tasks that definitely need to be accomplished or can be put off or eliminated. This sort of chart can also help in decisions about how responsibilities can be shared among family members. For example, your spouse might take over the grocery shopping. Deciding on the right balance between overdoing it and doing too little will take time and a lot of trial and error.

Doing things you enjoy can distract you from your illness. Focus on hobbies and activities you can still do and look for new ones to replace those you no longer can pursue. An example would be avoiding noisy shows outdoors in the heat and instead attending quiet shows in the cool indoors.

Take an inventory of your interests. People often forget about things they had an interest in but have not thought about for years.

Know your limitations. Substituting one activity for another may become necessary to maintain your sense of well-being.

Daily Life Tactics

Here are several basic tips to pace your life.

- Get adequate rest.
- Eat and drink right. Don't fast, and don't pig out.
- Try to keep a regular schedule.
- Get an appropriate amount of exercise, as prescribed by your physician.
- Avoid dehydration.
- Stay on your medication routine.

Mornings can be rough for people with orthostatic hypotension from chronic autonomic failure. Start slowly and use your knowledge. Studies have shown that autonomic failure patients can have a surprisingly large increase in blood pressure by drinking 2 glasses of water. You may find that drinking water about 15 minutes before getting out of bed in the morning helps you tolerate standing up. If your physician has advised you to increase your intake of fluid and salt, a glass of V8 or tomato juice might be helpful, as these drinks contain large amounts of sodium. Eating a large meal can shunt blood to the gut and decrease the ability to tolerate standing, and exposure to heat can decrease the blood pressure. If you attended a large church breakfast in the summer before standing still through a service, you could easily have a severe enough of a fall in blood flow to the brain to cause you to faint.

Exercise plays an important role in treating most chronic conditions, including dysautonomias. Staying in shape improves your sense of well-being. The veins in the legs

contain one-way valves that allow blood to flow towards your heart without allowing it to back up into the legs. Muscle surrounds deep veins in the legs and compresses these veins when you contract your leg muscles. Muscle pumping helps to keep blood moving towards the heart and upper body when you stand upright. You can do different types of exercise to assist your venous pump. You can tighten your calf, thigh, and buttocks muscles. Ask your physician about whether muscle pumping exercises would be appropriate for you.

Chronic illness, and especially chronic illness from an abnormality in the functioning of parts of the autonomic nervous system, can increase the susceptibility to anxiety, panic, and depression. There is nothing wrong with asking your doctor if you might benefit from medication to help you cope.

Avoid triggers that worsen your condition. Some triggers to keep in mind are:

- Hot environment (e.g., hot shower, sauna, Jacuzzi)
- Dehydration (not getting enough fluids)
- Emotional distress
- Over-stimulation (i.e., amusement parks, concerts, sporting events, video games, loud telephone ringing)
- Large meals
- Skipping meals
- Alcohol
- Skipping medications

Diet

Eating large meals tends to shunt blood toward the gut. This can worsen orthostatic intolerance and make a dysautonomia patient feel sluggish, tired, and worn out. Try eating smaller meals, more often. Check if sugary or starchy foods tend to worsen your symptoms. During eating, you might try elevating your feet to heart level and exercise your legs, to keep the blood from pooling. Just flexing your feet back and forth might provide a benefit.

For many patients with dysautonomias, a diet high in salt and fluids is necessary. Chicken noodle soup and V8 juice contain large amounts of salt. You should discuss salt intake with your doctor.

Environmental Temperature

Patients with a dysautonomia often have intolerance of heat or cold. If you have heat intolerance and plan on being outdoors during the summer, dress in cool, light clothes and limit the amount of time you spend in the heat.

You might feel faint taking a hot shower in the morning. Consider taking your shower prior to going to bed at night.

Compression Stockings/Abdominal Compression

Compression stockings can help patients who have excessive blood pooling in the lower half of the body when they stand up. If you use compression stockings, it can take some time to take

them on and off. You may find it easier to put your stockings on and off while lying in bed. Lying down may also keep you from becoming symptomatic while taking them off. A small amount of baby powder helps when putting them on. Compression stockings may be ineffective in preventing a fall in blood pressure standing.

You can buy affordable pantyhose to reduce pooling of blood in veins during standing. Try two pairs, one size smaller than what you would normally wear, and wear both at the same time. Abdominal compression has also been used to help prevent blood pooling when you stand up. Depending on your particular condition, a girdle one size too small can make a difference in how you feel. If wearing girdles or compression stockings isn't your style, try wearing bicycle pants.

Medic-Alert Bracelets

Patients with dysautonomias should wear a Medic-Alert bracelet. The back of the bracelet can state "See wallet." Inside your wallet you can have a piece of paper, laminated card, or electronic memory media about your condition, medications you take, allergies and sensitivities to medications, names and phone numbers of physicians, and emergency contact information for spouse or friend. For information on obtaining a Medic-Alert bracelet, visit <http://www.medicalert.com>.

Work

Whether or not you keep working is an individual decision

affected by a number of factors (e.g., severity of symptoms, type of work, financial situation).

It is likely your ability to work will be affected in some way by your illness.

It may be that you can no longer work full days, or you may no longer be able to travel as part of your job. If your job requires you to be on your feet all day, this may not be possible any more.

You might have to struggle with what if anything to tell your employer. Do you maintain your privacy, or let your employer know, so special accommodations can be arranged? This is a personal decision with no universal right or wrong answer. It may help to make a list of the pros and cons of disclosing your condition. Many things are going to affect your decision, including your specific work environment and job duties.

Work can involve episodes of emotional distress even in healthy people, so it's no surprise that it can worsen symptoms in someone with a dysautonomia.

You're probably going to have to make changes at work. This might mean setting more limits. It can be scary and frustrating to have to "slow down" at work. You might be afraid of what will happen and what people will think of you. You have to remember that if you don't slow down, you may be jeopardizing your health, which in the long run will result in being able to do even less. If you are contemplating taking time off from work, be sure to investigate all your options regarding

possible assistance. You might be able to telework.

There may come a time when you have to discontinue working altogether. The decision to leave the work world, whether temporarily or permanently, can be accompanied by a whole host of emotions, including anxiety, depression, guilt, or relief. To minimize anxiety associated with leaving work, structure your day (e.g., read books, listen to music, take a course over the internet, talk with friends), and try to learn something new. Make a list of your positive traits, to remind you that you are of value even if you're not working. Social networking with others in your situation can alleviate the sense of loneliness.

Travel

Driving is one of the most important aspects of our independence and often a necessity of everyday life. Discuss driving with your doctor. Your doctor can help to determine if your condition puts you at risk. If you are not able to continue driving, you will have to find ways others can help with your travel needs. Besides family, friends, and neighbors, your community may have programs. Your local Chamber of Commerce or United Way can give you information about public transportation and other programs.

Wearing sunglasses when you travel can reduce stimulus overload. You may notice that your symptoms don't seem as intense when you travel in the evening than in the daytime, or vice versa. Wearing earplugs can also help reduce the impact.

Depending on your specific condition, wearing a girdle,

compression stockings, or bicycle pants while traveling may be helpful. Have you ever noticed a change in your skin color when you stand upright? Rapid changes in the color of the skin are the result of blood. Compression garments may help you to keep blood in the upper part of the body when you are standing on line.

For many patients with dysautonomias, air travel can be a nightmare. It is best to discuss this with your physician. If your physician tells you it is all right for you to fly, discuss the following to see if they make sense for you:

- Drink extra fluids for at least a couple of days before departure.
- Eat a diet high in salt (V-8 juice, chips, pretzels, beef jerky, pickles).
- Avoid stressful, stimulating situations the day before or of departure. For instance, avoid going to the mall for last-minute shopping.
- Wear compression stockings and an abdominal compression garment.
- Wear earplugs or eyeshades.
- Ask your doctor about a medication to calm you and enable you to sleep during the flight.
- Fly with someone who knows your disorder.
- Request bulkhead seating, so you can elevate your feet to heart level during the flight.
- Request a wheelchair at your destination.
- Try to arrange a day of rest after your flight.

When to Ask for Help

It is not easy to find the right balance between independence and seeking help. At different points, you may need practical, financial, emotional, or physical help.

We all need help from others, whether we're healthy or not.

People often feel guilty asking for help from family and friends. Think about how things would be if the shoe were on the other foot. If your spouse or best friend had a chronic illness that required your assistance, would you resent a plea for help?

Explaining exactly how someone can help can provide a sense of relief to the helper, who may not know what to do. Don't assume that others can read your mind. You need to be clear in relating how you feel and what you need. You can make a list of the areas where you do and do not need assistance. Your friends, family, and caregivers need to do the same. You may not be sure what you want.

Social Activities

Staying involved in family and social activities as much as possible can help you cope with your illness. If you notice that these activities make your symptoms worse, then limit the time you spend on them. For example, if a family picnic were an all day function, you might plan on staying for only an hour or two.

You do not experience your illness in a vacuum. Those close to you are also impacted. They won't experience the same physical effects you do, but they will share other struggles (e.g., emotional, financial). This is a time of heightened stress and anxiety for the entire family.

Try to arrange a quiet time to sit down and talk with your family about issues related to your health. Explain clearly, and speak directly. Ask if they understand what you're trying to say, and clarify what is not clear. Listen to what they have to say. Try to express yourself in a non-threatening manner. Statements like, "Why do you always avoid me?" will probably make your loved ones feel attacked and cause them to become defensive. Instead, try to phrase your statement in neutral terms, such as, "Help me understand what you are going through. I feel like you don't want to be around me anymore and that hurts me. I miss being around you." Remember that no one will be put off by your expressing how you feel.

Your loved ones should also be allowed to express their feelings. They may be experiencing some of the same emotions you are, including anxiety and guilt. Anger and other negative emotions are also likely and normal. You and your family members can expect to feel hurt at times. Try to remember that these negative emotions are reactions to the situation and not to you yourself.

Attitude is a Battle

It is natural to have negative thoughts when your world seems to be crashing. People with chronic medical conditions are

susceptible to experience emotional distress, fear, depression, anger, frustration, anxiety, or other negative emotions.

Keeping a positive attitude will help you move on with your life. You must meet your challenges with determination. Blaming or attacking your physician, family, friends, or even God won't improve your health. Having a positive attitude might make things easier on your family, friends, and neighbors.

This sounds rather platitudinous. What practically can be done? Talking to others with the same condition can help. There is nothing wrong with discussing your anger, frustration, concerns, and fears. A health psychologist may help you acquire coping strategies. Some psychologists emphasize the importance of a "family session," where all members of the family can relate the effects that the illness has had on them. Keep in mind that the entire family is affected by your illness.

The key to happiness is appropriate expectations.

Take time to recognize your abilities and what you can do. For example, you may need help with grocery shopping but not with putting the groceries away. It may take time to discover what you can still do despite your limitations. Make small goals. Your goal today might be to walk from the bedroom to the kitchen. Next month it might be to clean the kitchen.

Referral to an Autonomics Specialist

Physicians in several fields of medicine see dysautonomia

patients, but unfortunately there are too few specialists in autonomic medicine.

Testing in a specialized autonomic function laboratory can help identify what form of autonomic involvement you have and speed development of an effective therapy program

Consider specialized testing.

You should not feel reluctant to talk to your physician about going to another facility for testing. You will likely find that your physician will actually encourage you to do so, because the visit may provide valuable and otherwise unobtainable information that your doctor can use to help you.

There are relatively few autonomic function experts and testing laboratories.

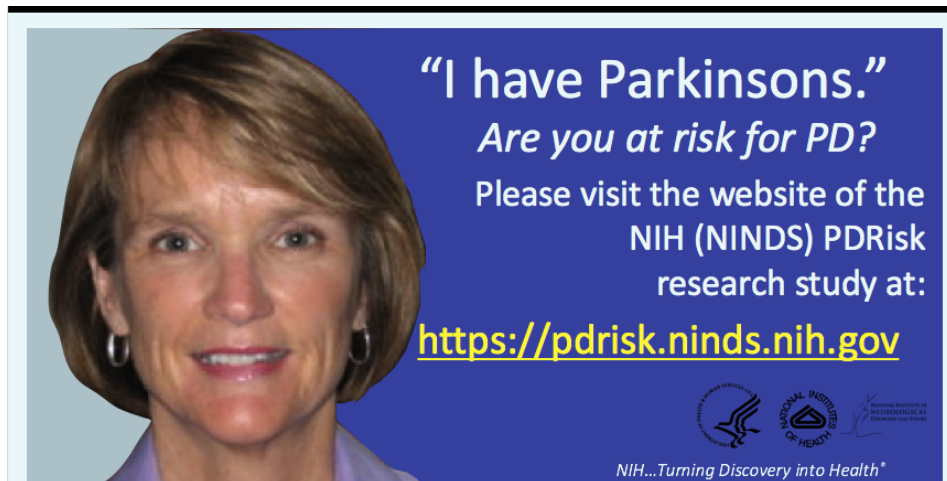
An educated general practitioner can take care of most of the management of dysautonomia patients. For a list of physicians and facilities in your area, try visiting the websites of the American Autonomic Society, at www.americanautonomicsociety.org; Dysautonomia International, at www.dysautonomiainternational.org; or the Dysautonomia Project, at thedysautonomiaproject.org.

Research Facilities - Should I Participate in a Study?

There are a limited number of academic medical centers in the

United States that conduct research on the autonomic nervous system. Some are at Vanderbilt in Tennessee, the Mayo Clinic in Minnesota, the Harvard system in Massachusetts, NYU in New York, the University of Texas in Dallas, and at the National Institutes of Health (the NIH) in Bethesda, Maryland.

Different centers study different types of dysautonomias. Patients are recruited to participate in research studies (also known as “protocols,” because the studies are designed, defended, approved, monitored, and reported according to pre-determined, detailed, written criteria). Each protocol has specific requirements, both for inclusions and exclusions. For a list of ongoing studies funded by the NIH you can contact the NIH’s Clinical Trials web site at www.clinicaltrials.gov.

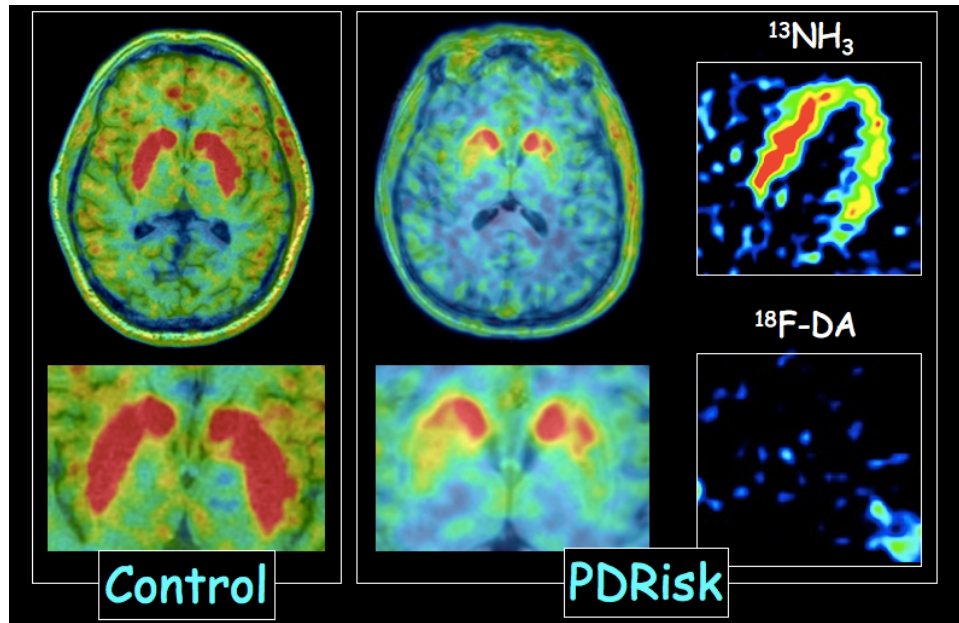


The NINDS PDRisk study is about biomarkers that may predict PD in at-risk individuals.

Participation in a research study may help you. Some benefits of participating in research are:

— You are seen by people who specialize in this area of

medicine. What may be unusual for your local physician may be routine for the investigators conducting the research.



This PDRisk study participant had biomarkers of nigrostriatal dopamine deficiency and cardiac sympathetic denervation that predicted the later development of PD and DLB. Early detection may enable protection of remaining neurons that are “sick but not dead.”

- You have the opportunity to learn more about what may be causing your symptoms. The testing could reveal important information about your condition that may not be available to your personal doctor.
- The medical institution may cover the costs of the research testing, which otherwise would be expensive if available at all.
- Even if you don’t benefit personally from your participation, you help researchers understand the illness better, making it

possible for them to devise better treatments.

It is important that you investigate the study thoroughly and review the consent information prior to participation. If you decide to participate in a study, keep in mind some of the possible limitations of the research:

- You may be required to stop taking your medications, for the doctors to see how you function without them.
- You may have to pay for travel.
- Some tests can be painful, uncomfortable, or not directly related to your problem.
- You may have to spend several days in the hospital.
- You may need pre-certification from your insurance company.
- You have to meet the criteria for participation in the study. Not everyone qualifies, and research patients may not be recruited once a quota is filled.
- Most important, you should understand that the usual primary focus of a research study is not to help a single patient but to learn more about the condition in general.

Research studies may not provide for your long-term care or follow-up.

This means that you will likely be returning to the care of your personal physician after participating in the research. Nevertheless, the researcher and the study results may help you and your doctor gain more knowledge about your condition and help devise an effective therapy program.

Physicians conducting research should not take the place of your local physician.

The research might give you immediate results, but alternatively it might take several months or even years before the research is completed and the results fully analyzed. You should have a clear understanding of what type of feedback to expect prior to your participation.

Keep educated about your condition. Passing along new information will help both you and your doctor. You will find that most physicians appreciate information provided them, especially if from a reliable source. Resource tools available today allow you a tremendous opportunity to stay abreast of new discoveries. You can find updates from a variety of sources (see the listing later in this section), patient conferences, books, and newsletters. The National Library of Medicine's websites offer you easy access to medical search engines that can also help keep you informed of new research discoveries.

CAREGIVING AND SUPPORT

Caregiving is taking care of and feeling responsible for another person, loved one, or family member. Family caregiving is

extremely important for coping with and successfully managing dysautonomias.

Family Caregiving

A family caregiver is someone who has primary responsibility for the well-being of another family member experiencing chronic limitations as the result of illness or injury. Caregiving has many facets, and each situation is different. The spectrum of caregiving responsibilities and capabilities may entail emotional, physical, social, practical, financial, logistical, and psychological care and support.

It is difficult to identify caregivers, because they don't feel that they are caregivers. Much of what caregivers do is out of love, respect, and being "family." The emotional and practical wear and tear on caregivers is real and needs to be understood. Caregiving doesn't come with a set of instructions, and after months or years caregiving can feel like a rut or trap. Without understanding the responsibilities of family caregiving many succumb to anger, resentment, confusion, and even physical ailments.

First and foremost is the need to recognize the role of being a caregiver. Not recognizing the caregiver role inherently prevents one from getting the understanding, help, support, and resources caregivers need.

Family caregiving is hard.

Why is caregiving so hard?

— Family caregiving involves routine and repetitive day-to-day psychological and social issues, economics, and perhaps physical care needs, and ongoing balancing act of work, household, and other activities.

— Family caregiving is not intuitive. Your maternal/paternal instincts and childrearing experience are not substitute training for family caregiving.

— There are numerous role reversals, such as kids caring for parents.

— People tend to wait for a crisis rather than plan strategically.

— Family caregivers feel transparent, with everyone focused on the care receiver and not appreciating the caregivers' efforts. Family caregivers can feel lonely, like they are in this by themselves and that no one understands what they are going through.

People rarely know what they don't know. Without instructions, planning, and clear understanding of the caregiver role, ongoing problems get harder to solve. Expectation management is a key ingredient in being a successful caregiver.

Caregiving for a dysautonomia patient is special.

Why is caregiving for someone with a dysautonomia different?

— People with a form of dysautonomia often don't look sick. Family, doctors, friends, schoolmates, and relatives have a hard time believing in the reality of the illness. Suspicions of malingering, psychosomatic illness, and “being lazy” are aroused continually.

— Dysautonomias typically are chronic illnesses. A chronic illness or disability such as congestive heart failure or stroke in an elderly person may mean 5-7 years of caregiving. When the onset is at birth or during adolescence, we may be talking about almost an entire lifetime. The younger the individual when illness strikes, the greater the scope of impact, including school, social life, relationships, future goals, responsibilities, work, and the entire family structure.

Kids don't think of themselves as caregivers, and they may be frightened and confused by the feelings they have. Most doctors and teachers do not think about children in this sort of role. If your children have this role, they need special support and a trusted outsider to talk to as well as Mom or Dad.

Spousal Caregiving by Men

For reasons that remain poorly understood, most patients with functional dysautonomias such as POTS are women. Spousal caregiving by men can be difficult. Seeing a wife or partner suffering and feeling inadequate to relieve the suffering can create a sense of emotional impotency. Physical sexual and other shared pleasures may be limited or lost, leaving the husband feeling lonely and unappreciated.

Lost opportunities for promotion, business travel, or increased

responsibility add to the burden. The potential alteration or dissolution of plans, dreams, and expectations of life imposed upon by chronic illness must be faced. The loss of an anticipated future must be grieved. The process of grieving goes through stages from denial to acceptance and may last for years. The partners may be at different stages on the road to acceptance.

Unresolved issues from the past with family or with spouse may become overwhelming. The role of spousal caregiver may not always be possible. Some will leave. Often, however, one may find courage, strength, and renewed love in long-term commitment to stay in the relationship.

Intimacy

Intimacy, which is important in a normal relationship, is greatly impacted and strained by the limitations of dysautonomias.

Intimacy is a major issue in caring for a spouse with a dysautonomia.

You can love someone and never be intimate or sexual with him or her.

You can have sex and never have intimacy with, or love for, the other person. You can love someone and have great intimacy without having physical sex. Whatever works for you is fine. The subject of intimacy is at the core of many of the issues couples face; it is inescapable for those dealing with chronic illness.

With dysautonomia you may look fine but feel awful. When you feel lousy, you don't feel sexy. That's a strain on any marriage or relationship.

You Are Not Alone

Whatever your beliefs, or whether you have a formal religion, having a sense of spirituality, an awareness of a guiding creative force, or a sense of transcendence can be a comfort and a coping mechanism. Use this as it fits for you.

It is likely that for a relationship to work in the setting of a dysautonomia will require outside professional help. If you are a family caregiver, recognize you are not alone. Others have worked through similar life- changing events. You must recognize your problems and actively seek your own help. No one else is automatically coming to solve them for you.

Major organizations with family caregiver support create an opportunity for defining roles, outlining responsibilities, sharing information, and gaining better understanding. Just as important as knowing what doctor to go to and what medication to try is to recognize the major burden of family caregiving with the knowledge that you are not alone. Understanding this is not only helpful to those with chronic caregiving responsibilities but also to spouses, children, other family members, friends, and the community.

Support Groups

Support groups are an invaluable tool to help deal with the consequences of dysautonomias. There can never be enough of sharing thoughts, helping one another, learning, and listening.

One of the best sources of help is a support group. A support group is a regularly scheduled, informal gathering of people whose lives are affected directly by a chronic illness or by the caregiver role. Members benefit from the peer acceptance and recognition of their common concerns and are grateful for the wisdom, insight, and humor of people in the same situation.

Learning coping techniques from others in a support group is extremely valuable. Patients with chronic illness need reliable guidance— understandable, clear, compassionate, and practical. Including the caregiver, significant other, or family members is especially important. Participants in support groups learn quickly from one another. Professional facilitators help accomplish even more.

Support groups are also a safe place to be heard and to listen and to understand symptoms and treatments. Support groups offer understanding on how to “reinvent yourself,” how to work with your healthcare team, how to communicate better with family and caregivers, and how to acquire effective strategies for daily living.

Today, physicians, social workers, rehabilitation specialists, neuropsychologists, and others refer patients to a recognized support group. Below is a listing of some dysautonomia

support groups and their web addresses. The numbers of such support groups and sites are growing rapidly.

- Dysautonomia International
(dysautonomiainternational.org)
- The MSA Coalition (multiplesystematrophy.org)
- The Dysautonomia Foundation, Inc.
(familialdysautonomia.org)
- The Dysautonomia Project (thedysautonomiaproject.org)
- Dysautonomia Information Network (dinet.org)
- National Dysautonomia Research Foundation (ndrf.org)
- Syncope Trust and Reflex Anoxic Seizures organization
(stars.org.uk)
- Dysautonomia Youth Network of America (dynakids.org)
- National Society for MVP and Dysautonomia
(mvprolapse.com)
- Dysautonomics (adiwebsite.org)
- Fight Dysautonomia.org (fightdysautonomia.org)
- American Dysautonomia Institute (dysautonomics.com)

Taking the initiative to begin a support group and following through is a major commitment but with many rewards. It doesn't take special training, but it does take effort, dedication, and some ingenuity. You may also find it to be very rewarding.

IDEAS FOR THE FUTURE

The field of dysautonomias may inspire new ideas that will influence the future of medicine. This is because of their complexity, chronicity, and multi-disciplinary, mind-body nature.

In large part I am presenting in this section a kind of philosophy or personal perspective, rather than a textbook discussion of symptoms, signs, tests, or treatments of specific conditions. I'm very curious to learn from you if we are of the same mind. You can reach me at goldsteind@ninds.nih.gov.

This section dwells on two implications of this perspective. First is the “mind-body” issue. Dysautonomias involve abnormalities at the border of the mind and body. In evaluating patients with a known or suspected form of dysautonomia, trying to separate the mental from the physical aspects is not helpful, either for diagnosis or for treatment.

Dysautonomias are generally chronic disorders of regulation. They involve many body systems at the same time and are treated with many drugs, which not only can interact with each other but also with other conditions that the patients may have. Dysautonomias can involve functional changes in several feedback loops, where there is no single abnormality at any particular place in the loops but dysfunction of the system as a whole.

The second implication is that some forms of dysautonomia are associated with chronic degenerative conditions such as Parkinson's disease or congestive heart failure, where long-term stress leads eventually to system breakdown by accumulated wear and tear. We are just beginning to understand how genetic

predispositions interact with life experiences and time to produce chronic diseases in old age.

I close this section with concepts of cybernetic medicine (I used to call this scientific integrative medicine, but this didn't fit with some people's expectations). Cybernetic medicine is a way of thinking about how the brain regulates the body's inner world, what goes wrong with that regulation in some disorders, and, given this knowledge, how to treat or even prevent disorders of regulation.

MIND-BODY DISORDERS

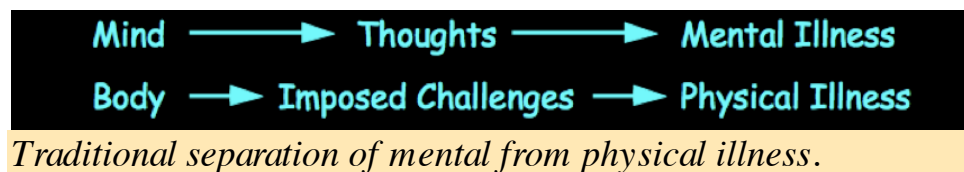
Dysautonomias are, possibly more than any other ailments, mind-body disorders.

Dysautonomias are mind-body disorders.

This is a difficult subject for both doctors and patients. The problem is the old notion that the body and mind are separate and distinct in a person, and so diseases must either be physical or mental. If the disorder were physical, it would be “real,” something imposed on the individual, while if it were mental, and “in your head,” it would not be real, but something created in and by the individual.

Distinctions between the “body” and the “mind,” the physical and mental, problems imposed on the individual and those in the mind of the individual, are unhelpful in trying to understand dysautonomias.

These notions date from the teachings of the Renaissance philosopher, Descartes. In my opinion they are outdated by now and inappropriate and unhelpful in trying to understand disorders of the autonomic nervous system.



Here is why. In this book you have learned about the “inner world” and the “outer world.” The mind deals with both

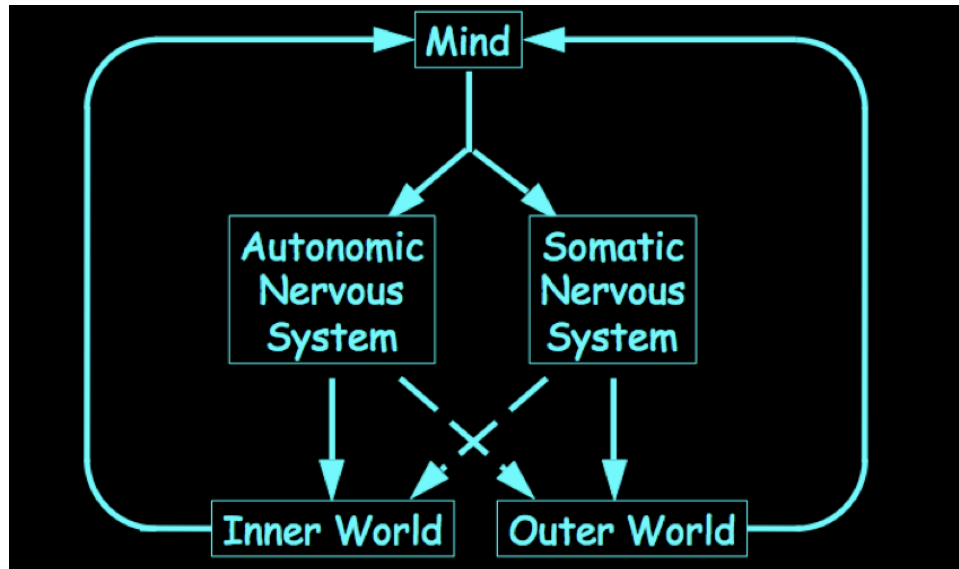
worlds, simultaneously, continuously, and dynamically in life. Conversely, both worlds affect the mind, and each individual filters and colors perceptions of the inner and outer world. For instance, there is no such thing as a person exercising without “central command,” to tense and relax specific muscles. At the same time, and as part of the same process, the brain automatically directs changes in blood flow to the muscles. The exercising muscle and changes in blood flow lead to information—feedback—to the brain about how things are going both outside and inside the body.

The autonomic nervous system operates exactly at the border of the mind and body. The brain both uses and depends on the autonomic nervous system for the internal adjustments that accompany every motion a person performs and every emotion a person feels.

The autonomic nervous system operates at the border of the mind and body.

You already know this, if you think about it. When you jog, for instance, the blood flow to the skin and muscle increases, the heart pumps more blood, you sweat, and you move more air. These are automatic features of the experience of exercising. Can you imagine exercising and not noticing these things?

It’s also true that virtually every emotion a person feels includes changes in the same body functions. For instance, when you are enraged, the blood flow to the skin and muscle increases, the heart pumps more blood, you sweat, your nostrils flare, and you move more air.



A systems approach to the mind-body issue.

From the point of view of the bodily changes, it would matter little whether these changes resulted from the physical experience of exercise or the mental experience of rage. Both situations involve alterations in the activity of components of the autonomic nervous system. Both situations involve changes in the inner and outer worlds. And if your autonomic nervous system were to malfunction, your reactions to either situation would not be regulated correctly; in either situation you could feel sick, look sick, and be sick!

A “systems” approach helps to understand dysautonomias. According to the systems approach, the mind simultaneously directs changes in the somatic nervous system and the autonomic nervous system, based on perceptions about what is going on in the inner world and the outer world.

Note that the autonomic nervous system affects both the inner world and outer worlds. For instance, if a person looked pale, because the blood had drained from the face, and were sweaty, trembling, and mumbling incoherently, other people would likely react to these signs of distress and ask, “Are you OK?” And it is well known that strong emotions, probably via adrenaline release, can energize an individual. Recall that one of the entries under weightlifting in the Guinness Book of Records referred to a 123-pound mother who summoned the strength to lift the front end of a car after a jack had collapsed and the car had fallen on her child.

Analogously, the somatic nervous system can affect the inner world via the autonomic nervous system. For instance, you can voluntarily increase your blood pressure any time you want, by clenching a tight fist, or dunking your hand in ice cold water.

How would a systems approach help to understand a dysautonomia? A malfunction at almost any part of the system could lead to alterations in activities of components of the autonomic nervous system. For instance, if there were no feedback to the brain about the state of the blood pressure (part of the inner world), then there would be an inability to keep the blood pressure within bounds, by changing the activity of the sympathetic noradrenergic system. If there were no feedback about the extent of physical exercise, there would also be an inability to adjust the blood pressure and blood flows appropriately. Of course, if there were a failure of the autonomic nervous system itself, this would also interfere with regulation of the inner world, but there would also be difficulty in dealing with the outer world, manifested by problems like exercise intolerance or an inability to tolerate standing for a

prolonged period (orthostatic intolerance). Finally, if the person had a psychiatric disorder such as panic/anxiety, then the inappropriate emotional experience of fear would be linked to both autonomic nervous system and somatic nervous system changes.

A clinician's ability to treat a dysautonomia successfully also benefits from a systems approach. Treatments at any of several steps might help, but the best place in the system to insert a treatment would be the step closest to where the cause is—if there were only one.

CYBERNETIC MEDICINE

The Changing Face of Disease

The Human Genome Project and its descendants have produced a huge fund of information about the normal and diseased human genome. This information is not static but is expanding rapidly, due to identification of single nucleotide polymorphisms, splicing variants, whole gene or nucleotide sequence repetitions, variations in genes encoding transcription factors and promoters, multiple simultaneous genotypic changes, genetic imprinting, mosaicism, and stress and other epigenetic effects on chromosomes. We also are now seeing the introduction of computerized applications to analyze that information.

- Chronic
- Degenerative
- Complex, multi-system
- Long pre-symptomatic phase
- Genetic-environmental interplays
- Treatment-disease interactions

The changing face of disease

Even as genetic information-gathering has expanded, however, the very nature of disease has changed.

The era of “strep throat medicine” has come to an end. The era of chronic, complex disorders of regulation has begun.

These involve derangements of multiple body processes, drug treatments, and interactions among the derangements and the drugs, posing enormous personal and societal burdens. The notion that diseases have simple, single causes that can be cured with a “magic bullet” like penicillin does not apply to dysautonomias or to a large number of other disorders of regulation of the “inner world” inside the body.

For developmental diseases of specific, isolated body processes, genotypic or gene expression data might suffice to identify the pathophysiologic pathways from etiology to clinical phenotype in intra-uterine or postnatal development.

Much less clear is how genetic changes already present at birth interact with individual life experiences to lead to multi-system degenerative disorders decades later.

Over the years I’ve developed a way of thinking that takes these developments into account. In the past I called it “scientific integrative medicine,” but integrative medicine has been used by others to mean healing-oriented medicine that takes into account the whole person and involves both conventional and alternative treatment approaches; and so I’ve adopted the term, “cybernetic medicine.”

Cybernetic medicine is not a discipline, a group of disorders, or a method of treatment, but a way of thinking or an approach that emphasizes disorders of the multiple interacting systems that regulate the “inner world” of the body.

Cybernetic medicine uses systems concepts to explain diseases in terms of interactions among genetic makeup, life experiences, drug treatments, and time, with the goal of developing strategies to treat, prevent, or palliate multi-system disorders.

Dysautonomias may be a perfect example of how applying concepts of cybernetic medicine can advance medical science and patient care in the post-genome era.

More generally, concepts of cybernetic medicine have the potential to forge important links between modern systems biology and classical integrative physiology.

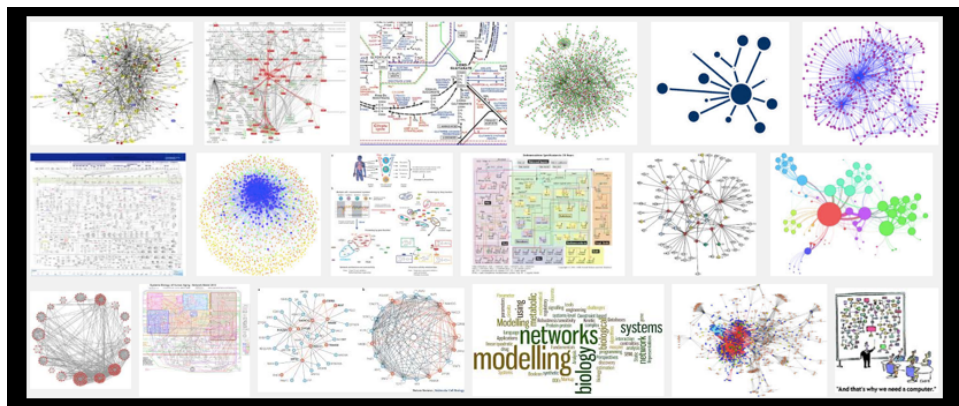
For most of our existence we believe in our essential sameness day to day and rarely notice the internal workings that constitute the political affairs of the inner world. Things inside seem to stay in a steady state so well, for so long. This applies especially to factors that the autonomic nervous system regulates, such as body temperature, blood levels of key fuels, concentrations of red blood cells in the bloodstream, amounts of electrolytes, the rate of the heartbeat, blood flows to organs, and blood pressure. These and many more “variables”

normally don't vary much. These steady states do not happen by chance. They depend on complex coordination by the brain. The brain regulates the inner world, to maintain apparent constancy despite continual change.

The brain does so via negative feedback systems. For most of our lives we can cling to our belief in sameness because the brain tracks many monitored variables, by way of internal sensory information, and acts on this information to maintain levels of monitored variables at controlled, steady values by modulating numerous effectors that work simultaneously, in parallel.

A foundation of cybernetic medicine is the negative feedback loop.

Cybernetic medicine finds its roots in the issue of how higher organisms maintain their integrity despite the vicissitudes of life.



Systems biology has focused on networks in complex webs more than on hierarchies and negative feedback regulation.

You might at first think that cybernetic medicine is merely a specialized, applied form of systems biology. Actually, the term, “systems biology,” was rarely used in medical scientific reports before the beginning of the 21st century, whereas the conceptual underpinnings of cybernetic medicine originated with Claude Bernard in the mid-19th century and Walter B. Cannon in the early 20th century.

Systems biology has been defined variously. One definition is the study of dynamic interactions within biological networks. These interactions can give rise to “emergent” properties unpredicted by any of the components assessed in isolation, and in this sense systems biology can be viewed as “holistic” or “integrative.”

It seems to me that advocates of systems biology have so far not considered sufficiently integrative physiological concepts such as homeostasis, negative feedback-regulated systems, and redundant effectors. Cybernetic medicine can link systems biology with integrative physiology.

Negative Feedback Regulation

Negative feedback loops are required for maintaining homeostasis. This notion follows directly from Bernard’s *milieu intérieur* and Cannon’s homeostasis. Diseases and disorders can be understood in terms of loss of regulation of internal monitored variables because of disruption or declining efficiency at stations in negative feedback loops. Mathematical models incorporating afferent information, homeostats, effectors, etc., can be used to predict the roles of factors such as

stress, adaptation, allostatic load, and resilience on the development and manifestations of acute and chronic disorders.

You have learned that when a monitored variable is regulated by a negative feedback loop, the monitored variable reaches a stable steady-state level and that disruption of a negative feedback loop always increases the variability of the level of the monitored variable. Decreased efficiency of negative feedback regulation of monitored variables of the body's inner world therefore threatens homeostasis.

- Negative feedback regulation

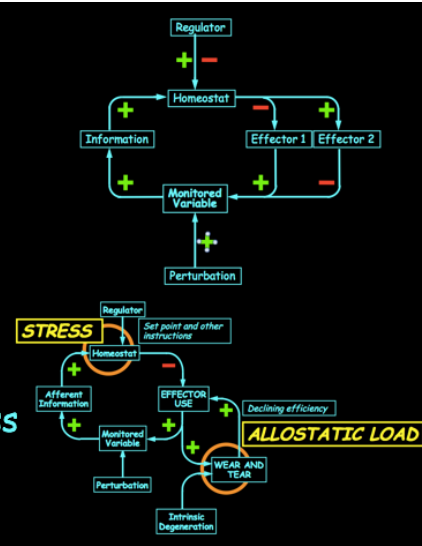
- Multiple effectors

- Shared effectors

- Positive feedback

- Homeostatic definition of stress

- Allostatic Load



Some elements of cybernetic medicine

The situation in heart failure illustrates this phenomenon. As we age, the efficiency of heart muscle function declines—in some sooner than in others, depending on hereditary predispositions and life exposures. As intrinsic heart muscle function declines, the brain senses the decreased pumping ability and directs a compensatory increase in sympathetic noradrenergic system outflow to the heart. This augments the

delivery of norepinephrine to its receptors on heart muscle cells, keeping the cells' contractility and the heart's ejection of blood within normal limits. Bombardment of heart muscle cells by norepinephrine, however, decreases the threshold for the development of abnormal heart rhythms (arrhythmias). When an arrhythmia occurs, the heart instantaneously pumps less blood. The brain directs a further increase in norepinephrine release from nerves in the heart, but this augments further the automaticity of the cells. When segments of heart muscle begin to contract autonomously, rather than synchronously, the heart ceases to function as a pump, and the patient suddenly, often unexpectedly, dies.

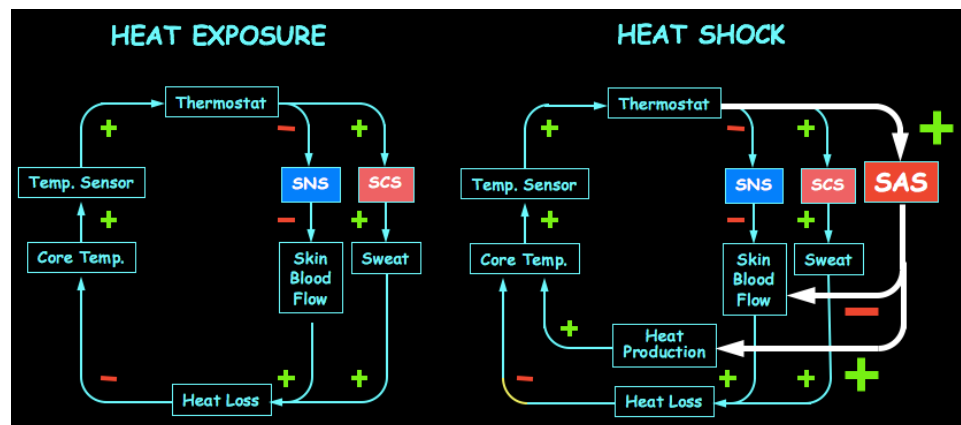
A goal of cybernetic medicine is to devise means to detect early or even prevent such a catastrophic positive feedback loop. Even after symptoms of heart failure develop, judicious treatment with drugs that moderate effects of norepinephrine could enhance survival.

In patients with chronic diseases of almost any sort, the inner world breaks down eventually. A key way this happens is by development of positive feedback loops. Positive feedback loops threaten organismic integrity and can lead to rapid decompensation and even death.

Here are some scenarios in which transition from a negative feedback to positive feedback situation is harmful.

— A footballer practicing in full uniform in the heat releases adrenaline, which constricts skin blood vessels and augments heat production in the body, producing heat exhaustion, which releases more adrenaline, bringing on heat shock.

- Heart failure stimulates the sympathetic nervous system and the renin-angiotensin-aldosterone system, which increases fluid retention and growth of heart muscle, worsening the heart failure.
- Chest pain from coronary ischemia due to coronary artery disease evokes distress, stimulating the adrenomedullary hormonal system, increasing the work of the heart and worsening the ischemia.
- Orthostatic hypotension from failure of the sympathetic noradrenergic system causes lightheadedness, a fall, fracture of a hip, and prolonged bed rest in traction, worsening the orthostatic hypotension when the patient tries to get up.



The transition for heat exposure to heat shock can be explained by initiation of positive feedback loops.

- Loss of dopamine terminals in the nigrostriatal system in the brain increases pathway traffic to the remaining terminals, accelerating dopamine turnover and thereby production of toxic by-products of dopamine metabolism, increasing the rate of loss

of dopamine terminals, eventually manifesting clinically as Parkinson's disease.

— A viral illness causes dehydration, orthostatic intolerance, and compensatory activation of the sympathetic noradrenergic system, resulting in postural tachycardia syndrome (POTS). Because of ongoing fatigue, the patient spends more time in bed, the muscles atrophy, and the blood volume declines, resulting in worsening of orthostatic intolerance and exaggeration of POTS symptoms.

The timing and rapidity of system failure from positive feedback loops depend on dynamic interactions between usage experience of the system and built-in manufacturing and design characteristics. In the body, the occurrence, timing, and rapidity of progression of degenerative diseases depend on interactions between environmental exposures and genetic predispositions. The concepts of allostasis and allostatic load provide a framework for linking stress, distress, and acute and chronic dysautonomias.

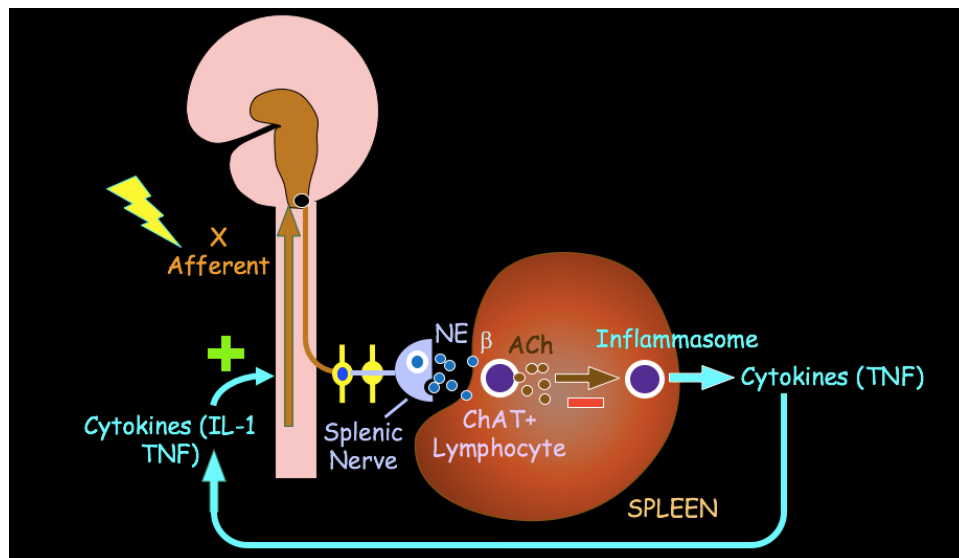
BIOCYBERNETICS

Norbert Wiener coined the term, “cybernetics,” the science of automatic communication and control systems. Biocybernetics refers to automatic communication and control systems in living organisms.

Wiener distinguished two forms of biocybernetics, medical biocybernetics and neurocybernetics. In medical biocybernetics, “homeostasis is the main consideration,”

whereas neurocybernetics mainly involves “the pathways of actions via sense-organs, neurons and effectors.”

Three types of current experimental therapeutic approaches for disorders of homeostasis can be viewed as biocybernetic. Carotid sinus stimulation and renal sympathetic radiofrequency ablation may attenuate refractory hypertension; IV infusion of norepinephrine or an automated abdominal binder may mitigate neurogenic orthostatic hypotension; and vagus nerve stimulation, by directly or reflexively evoking effects on elaboration of cytokines, may be useful to treat conditions involving autoimmunity such as rheumatoid arthritis.



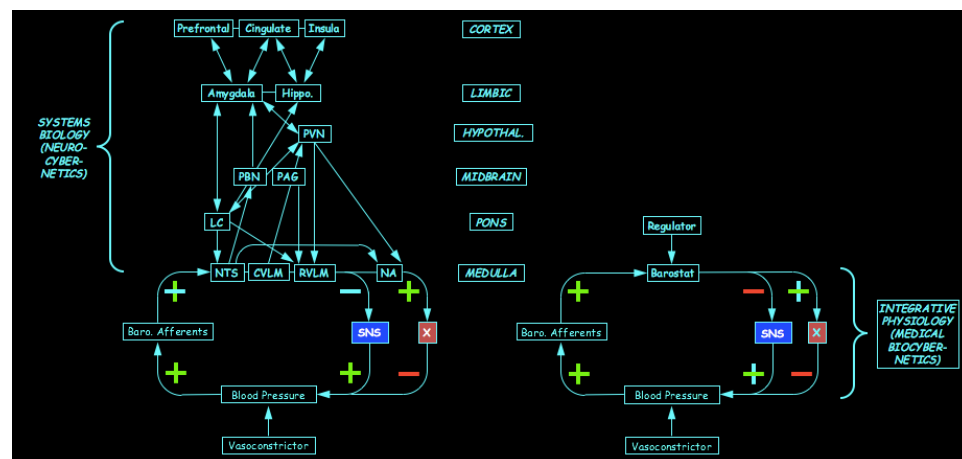
Vagus nerve stimulation is a biocybernetic approach to treat inflammatory disorders.

I envision further evolution of the homeostasis theory to encompass integration of autonomic nervous with behavioral, endocrine, autocrine/paracrine, and cytokine effectors. The general proposal is that integration of these systems mediates

automatic adjustments maintaining health and that disintegration of these systems causes disorders of regulation in disease. It is time to extend the meaning of “autonomic.”

Central Neural Hierarchies

Cybernetic medicine recognizes that in higher organisms the brain dominates in regulation of the body’s inner world. In humans this regulation occurs via a hierarchy of centers in the brain.



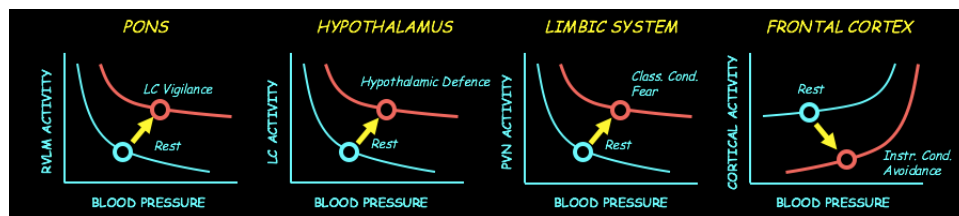
The diagram on the left depicts some inter-connections among nodes in the central autonomic network that, taken together, constitute a good regulator for blood pressure regulation by the sympathetic noradrenergic system (SNS) and parasympathetic cardiovagal system (X). The diagram on the right depicts reflexive blood pressure regulation by the same SNS and X effectors via a metaphorical “homeostat,” the barostat.

Here is an example of how a systems biology approach and an integrative physiology approach would apply to homeostatic

regulation of blood pressure during infusion of a vasoconstrictor and a vasodilator.

At the lowest level of regulation there is a simple input-output relationship between sympathetic noradrenergic system (SNS) outflow and blood pressure.

Increased activity in the RVLM changes the relationship between SNS outflow and blood pressure. Increased activity in the pontine locus ceruleus (LC) as part of a vigilance reaction alters the relationship between RVLM outflow and blood pressure.



Allostatic changes in input-output relationships at different levels of the brain produce effects that give the appearance of an altered “barostat” setting.

At hypothalamic and limbic system levels, there are yet other input-output relationships, for emotional, primitive behavioral, or arousal states. For instance, stimulation of the PVN attenuates responses of neurons of the medullary nucleus of the solitary tract (NTS) that are activated when phenylephrine is injected to increase blood pressure. Increased PVN activity as part of a “defence reaction” alters the relationship between rostral ventrolateral medullary (RVLM) activity and blood pressure. Increased activity in limbic system centers such as the amygdala and hippocampus as part of classical fear

conditioning alters the relationship between PVN activity and blood pressure. Pavlovian conditioning is close to cause-controlled regulation, in that the organism is reacting in anticipation of future situations.

Finally, at higher cortical levels there are yet other input-output relationships for executive functions, psychosocial restraint, operantly conditioned behaviors, and simulations. Release from cortical restraint as part of an instrumentally conditioned avoidance response alters the relationship between cortical activity and blood pressure. All these processes contribute to the reflexive response to the vasoconstrictor.

Overall the system operates as if there were a “barostat.”

The brain controls levels of many internal monitored variables in parallel—analogous to a computer’s multitasking—each via a homeostatic system. As a corollary, pathophysiologic mechanisms of a variety of complex, mind-body, multi-system disorders involve, and may result from, altered central control.

Plasticity

The brain’s plasticity enables modifications in the step-by-step instructions for organ and systemic processes. According to the concept of allostasis, set-points and other elements of response algorithms vary depending on instinct, imprinting, learning, perceptions, and even simulations of future events by the brain.

The theoretical biologist, Danko Nikolic, recently introduced the term, “practopoiesis.” Practopoiesis is an arrangement for

achieving intelligence through adaptation, in which mechanisms laying at a lower level of organization, by their operations and interaction with the environment, enable creation of mechanisms laying at a higher level of organization. This interesting conceptual framework has not yet been tested experimentally.

Systems Medicine

Cybernetic medicine is medical. Its overall mission is to understand, rationally treat, retard the progression of, or even prevent disorders and diseases.

The systems that maintain the stability of the inner world eventually degenerate, and as their efficiencies decline, the likelihood of deleterious, self-reinforcing positive feedback loops increases, threatening organismic stability and survival. Clinicians manage patients by exploiting negative feedback loops and attempting to forestall or counter positive feedback loops. Moreover, the medications and treatments clinicians prescribe interact with their patients' internal systems. Multiple, simultaneous degenerations, combined with multiple effects of drugs and remedies and myriad interactions among the degenerations and the treatments constitute the bulk of modern medical practice. Cybernetic medicine offers a schema and vocabulary for approaching the imposing complexity of managing patients.

“Integrative medicine” has gained cachet recently. The word, “integrative,” has been used synonymously with holistic, complementary, or alternative. The cybernetic medicine

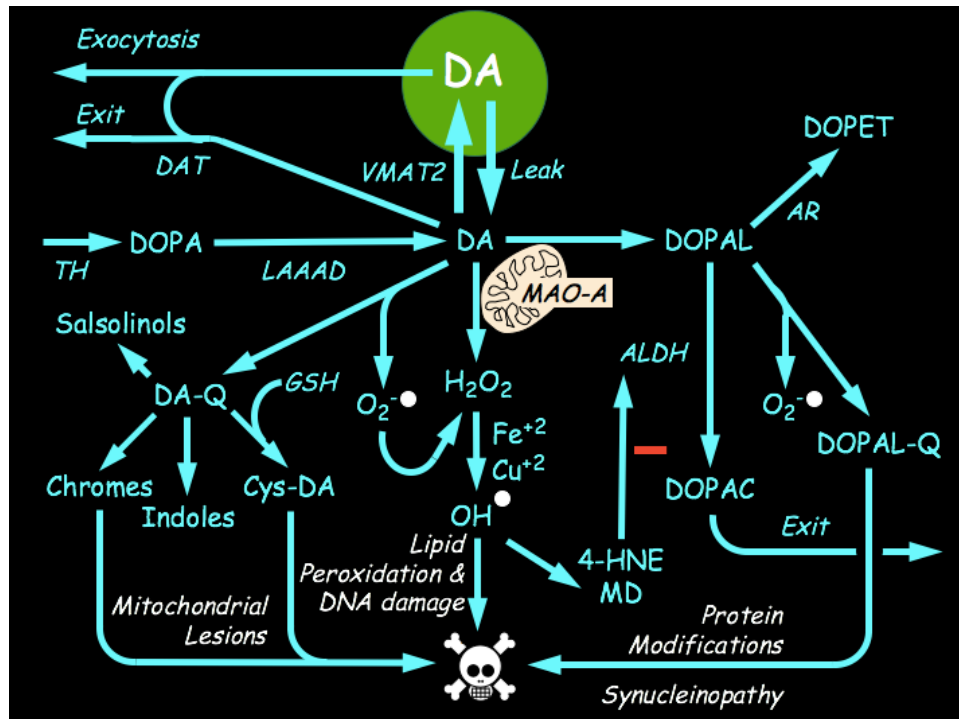
approach, however, actually fits quite well with conventional clinical science and integrative physiology. The emphasis is not on rationalizing or testing the efficacy of holistic or alternative treatment programs but on viewing the body as a governed system of systems.

AUTOTOXICITY

Several neurodegenerative diseases involve loss of catecholamine neurons—Parkinson’s disease (PD) is a prototypical example. Catecholamine neurons are rare in the nervous system, and why they are vulnerable in PD and related disorders has been mysterious.

One explanation is that catecholamine neurons are susceptible *because* they are catecholamine neurons. “Autotoxicity” refers to inherent cytotoxicity of catecholamine metabolites in the cells in which they are produced. The essence of the catecholamine “autotoxicity” theory is that catecholamines can be turned into “suicide chemicals” that will kill the neuron if they are allowed to oxidize and if the toxic oxidation products aren’t detoxified efficiently.

In general there are two mechanisms that prevent catecholamines from building up in the cytoplasm. The first is sequestering them in storage vesicles. In the vesicles they are inert, but catecholamines leak from the vesicles into the cytoplasm continuously during life. They are recycled back into the vesicles by the type 2 vesicular monoamine transporter (VMAT2). The second detoxification mechanism is two enzymes in series. Catecholamines undergo enzymatic oxidation catalyzed by monoamine oxidase (MAO) in the outer mitochondrial membrane. The immediate product is a highly toxic aldehyde called DOPAL; however, DOPAL is rapidly detoxified by the enzyme aldehyde dehydrogenase (ALDH). ALDH converts DOPAL to DOPAC, an acid that is non-toxic and rapidly leaves the cell.



Overview of the catecholamine autotoxicity theory. Cytoplasmic dopamine (DA) buildup is toxic, via enzymatic oxidation by MAO-A to form hydrogen peroxide and DOPAL and via spontaneous oxidation to form 5-S-cysteinyl dopamine (Cys-DA) other compounds. VMAT2 and the series of MAO-A and ALDH keep cytoplasmic DA levels low; however, Parkinson's disease involves both decreased VMAT2 and ALDH activity, setting the stage for multiple positive feedback loops.

The “catecholaldehyde hypothesis” is a hypothesis derived from the autotoxicity theory that may apply to the pathogenesis of PD. According to the catecholaldehyde hypothesis, long-term increased build-up of DOPAL, the catecholaldehyde metabolite of dopamine, causes or contributes to the eventual death of catecholamine neurons. Consistent with the catecholaldehyde hypothesis, in PD there is decreased

efficiency of vesicular sequestration, decreased activity of ALDH, and DOPAL accumulation; however, there is no evidence so far that in PD the DOPAL buildup actually kills the neurons.

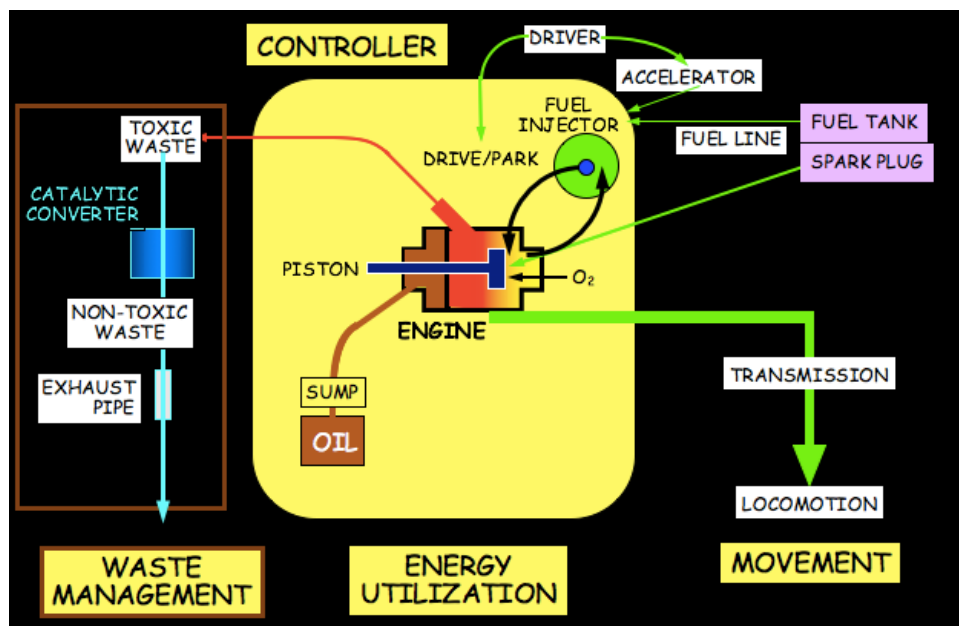
Lewy bodies are a neuropathologic hallmark of PD that contain precipitated alpha-synuclein. Bases for the tendency of alpha-synuclein to precipitate in the cytoplasm of catecholaminergic neurons have also been mysterious. DOPAL potently oligomerizes and aggregates alpha-synuclein. This could be a key link between alpha-synucleinopathy and catecholamine neuron loss in Lewy body diseases.

The overall concept is that products of catecholamine oxidation, such as DOPAL, and alpha-synuclein are nodes in a complex nexus of interacting homeostatic systems. Dysfunctions of several processes, including decreased vesicular sequestration of cytoplasmic catecholamines, decreased ALDH activity, and oligomerization of alpha-synuclein, lead to conversion from the stability afforded by negative feedback regulation to the instability, degeneration, and system failure caused by induction of positive feedback loops. These dysfunctions result from diverse combinations of genetic predispositions, environmental exposures, stress, and time.

The notion of catecholamine autotoxicity has several implications for treatment, disease modification, and prevention. Conversely, disease modification clinical trials would provide key tests of the autotoxicity theory.

The Getaway Car Analogy

I use the analogy to a bank robber's getaway car to teach about how catecholaldehydes, the products of enzymatic deamination of cytoplasmic catecholamines, can explain the aging-related loss of catecholamine neurons in PD and other neurodegenerative diseases.



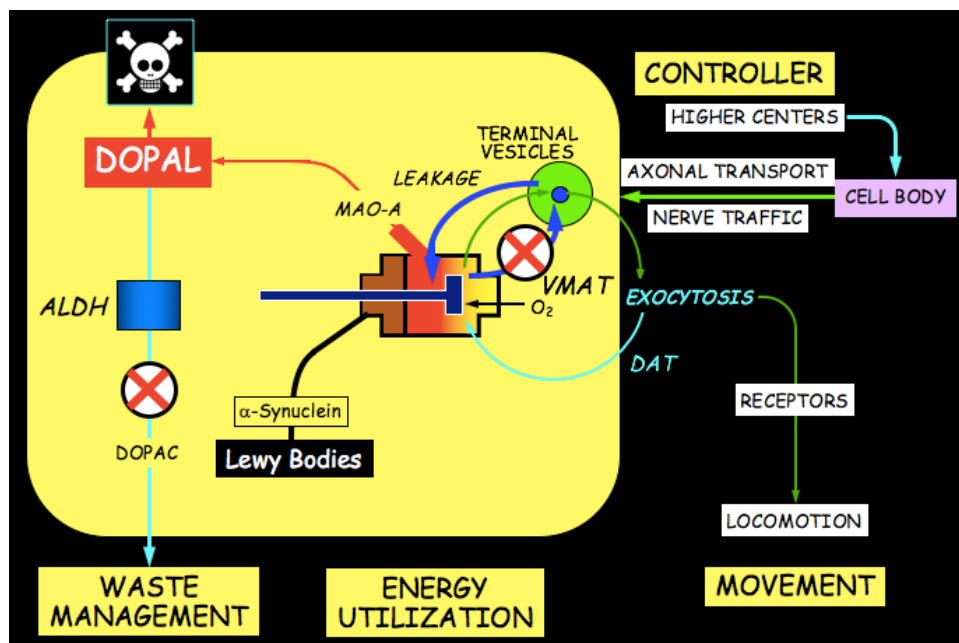
Concept diagram for the "getaway car" analogy

The engine of a car converts energy to movement. There is a controller—the driver—that regulates this process. The fuel injector squirts fuel into the combustion chamber, where the fuel is combusted. When the car is idling, the fuel injector squirts the gasoline into the combustion chamber at a slow, continuous rate.

Combustion is an oxidative process. The immediate products

of the combustion may be harmful, but they are converted to non-toxic waste products by the catalytic converter, which exit the car via the tailpipe. For the sake of analogy, let's say the amount of fuel in the combustion chamber is limited by recycling back into the fuel injector. The pistons in the engine are lubricated by oil supplied by a reservoir crankcase.

The neurons in an organism convert energy to movement. A complex hierarchy of centers regulate the process, which is coordinated with many adjustments mediated by catecholamines. Under resting conditions catecholamines in the vesicles leak continuously into the cytoplasm, where they are oxidized spontaneously (auto-oxidation, if you'll excuse the pun) or enzymatically (by monoamine oxidase-A, or MAO-A).



The getaway car analogy used to convey the catecholaldehyde hypothesis

The immediate products of the oxidation are toxic. In

particular, DOPAL is the toxic aldehyde produced when MAO-A acts on cytoplasmic dopamine. The harmful byproducts of catecholamine oxidation are to a large extent detoxified by enzymes, the catalytic converters of the neurons. DOPAL is detoxified by ALDH converting DOPAL to DOPAC. The non-toxic waste product then exits the cell.

The type 2 vesicular monoamine transporter (VMAT2) recycles the cytoplasmic catecholamines, so that levels of cytoplasmic catecholamines are kept very low. The cytoplasm of the neurons contains a variety of dissolved proteins, including the protein, alpha-synuclein.

What if the getaway car had a faulty catalytic converter? The toxic byproducts of combustion might back up and potentially harm the engine. What if there were deficient recycling of the gasoline back into the fuel injector? Then there would be more production of the toxic byproducts of combustion.

Analogously, what if a dopaminergic neurons had decreased ALDH activity? Then DOPAL would tend to accumulate. What if there a vesicular storage defect? Then for a given rate of dopamine synthesis in the cytoplasm, there would be a higher rate of DOPAL production.

If you were a bank robber your getaway car would be kept idling at the curb outside the bank. If the ignition were off, it would take longer for you to get away just when you had to, and if the ignition happened to fail at that crucial time, that would be the end of your career as a bank robber. Suppose you decided not to rob the bank on that particular day and decided to “case the joint.” The car would be kept idling. After several

months of reconnaissance and many fuel refills, just from the wear and tear of having had the car in idle all that time, the engine's life span probably would be shortened because of a buildup of harmful deposits—gunk—inside. The engine might fail completely.

If you did a “post-mortem” on the engine and crankcase, you would find gunk deposits. No amount of analysis of the gunk would pinpoint the root cause of the engine failure. Maybe the catalytic converter had a design or manufacturing flaw, or something interfered with the fuel injector recycling the non-combusted fuel, or the oil had the wrong viscosity, or the driver habitually “floored” the accelerator. You wouldn't be able to tell.

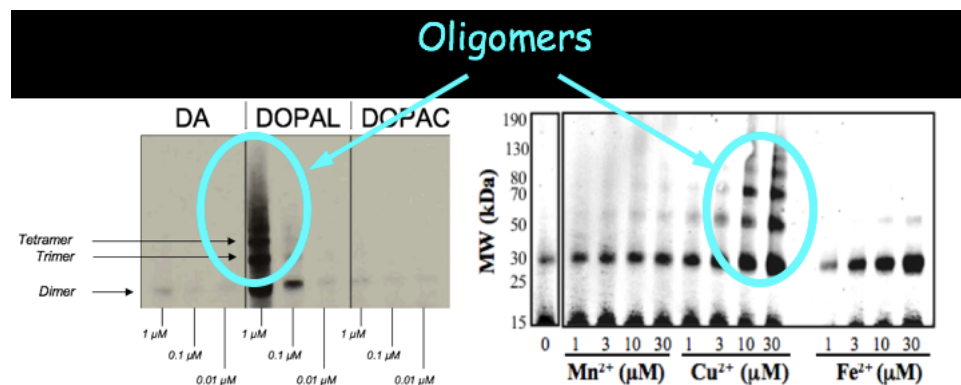
Even if none of these factors alone would have ever caused a problem in the normal life span of the car, together they could have built up sufficient gunk to kill the engine. Despite the extraordinarily complex design and manufacture of the car, and its obvious importance for you, you might well decide to tow it to the junkyard and sell it for scrap. Nevertheless, you could still decide in the end that it had been worthwhile to keep that car idling at the curb.

Catecholamine neurons are like little getaway car engines.

Catecholamine neurons like nigrostriatal dopaminergic neurons and cardiac sympathetic noradrenergic neurons are “on” continuously, in the sense that dopamine is being synthesized in the cytoplasm, and dopamine and norepinephrine (which is

synthesized in the vesicles from dopamine taken up from the cytoplasm) are always leaking from the vesicles into the cytoplasm. Some of the cytoplasmic dopamine that escapes vesicular uptake auto-oxidizes to dopamine quinone, which in turn is converted to 5-S-cysteinyl-dopamine, dopaminechrome, or 5,6-dihydroxyindole, all of which are toxic.

Most of the cytoplasmic dopamine that escapes vesicular uptake is oxidized enzymatically to form DOPAL and hydrogen peroxide, both of which are toxic. If there were a deficiency of ALDH, DOPAL would build up, and if there were a vesicular storage defect, then for a given rate of dopamine synthesis the rate of DOPAL production would be increased. Evidence for all these abnormalities has been obtained.



DOPAL oligomerizes alpha-synuclein, especially in the setting of divalent metal cations.

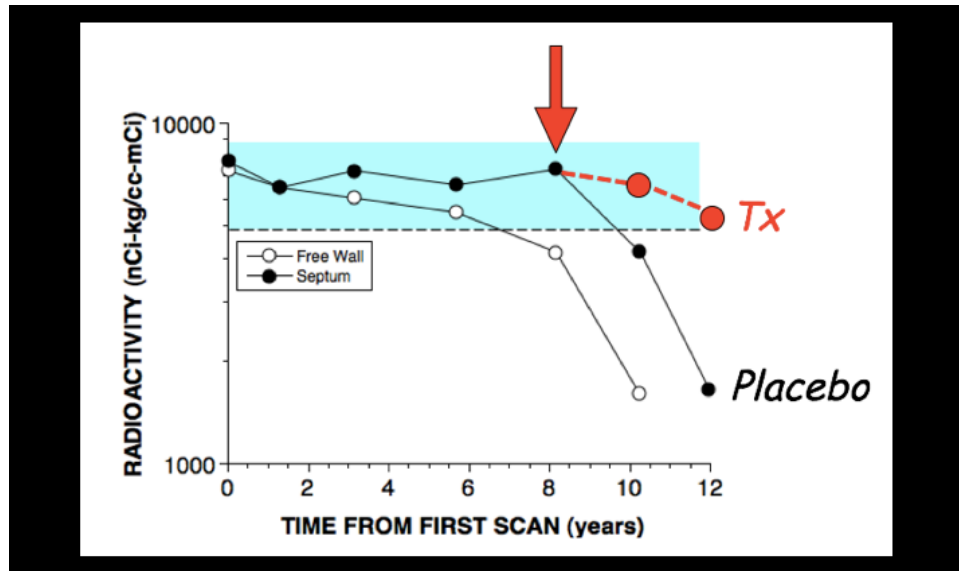
What about the “gunk” in the getaway car engine? DOPAL potently oligomerizes and aggregates alpha-synuclein. Lewy bodies, the pathologic hallmark of Parkinson’s disease, contain abundant precipitated alpha-synuclein.

The high rate of leakage of catecholamines from vesicles into the cytoplasm, and the high rate of reuptake back into the vesicles by way of VMAT2, would at first seem like a waste of energy. What good could this do, as opposed to having a stable pool in vesicles that don't leak? My colleague at the NIH for many years, Graeme Eisenhofer, came up with an insightful explanation, which he calls “gearing down.” If there were a stable pool of vesicles, then an emergency requiring sustained norepinephrine release would rapidly dissipate that pool. It would be impossible for synthesis of norepinephrine from scratch (the rate of which can only about double) to keep up with the irreversible loss of norepinephrine from the tissue (the rate of which can go up many-fold). But if there were continuous leakage of norepinephrine from the vesicles, and continuous replacement of the norepinephrine by ongoing synthesis, then the organism could maintain a high rate of release of norepinephrine for a much longer time.

Randolph M. Nesse and George C. Williams, in their thought-provoking book, *Why We Get Sick*, ask, “If senescence so devastates our fitness, why hasn’t natural selection eliminated it?” Williams provided an answer in 1957 in his pleiotropic theory, according to which genes causing senescence have early benefits. In lay terms, “senescence is the price we pay for vigor in youth.” Improved resilience and anti-fatigue in young reproducers comes at the cost of autotoxicity, accumulation of allostatic load in catecholaminergic neurons that may eventually precipitate positive feedback loops and kill those neurons in neurodegenerative disease such PD.

The catecholaldehyde hypothesis and getaway car analogy lead straightforwardly to testable ideas about how to delay the onset

of or slow the rate of aging-related loss of catecholamine neurons.



The catecholaldehyde hypothesis predicts that in a patient with Parkinson's disease and partial cardiac sympathetic denervation, treatment to inhibit enzymatic and spontaneous oxidation of catecholamines should slow the disease process.

First, inhibit MAO-A, since this would decrease formation of the toxic metabolite, DOPAL.

Second, treat with an anti-oxidant that is bioavailable to catecholaminergic neurons, since this would attenuate spontaneous and enzymatic oxidation of cytoplasmic catecholamines and interfere with synuclein oligomerization.

FLIPPING THE CLINIC

The term, “flip the clinic,” refers to an initiative by the Robert Wood Johnson Foundation (RWJF). RWJF considers this to be less a full-fledged program than a “conversation” in progress.

Flipping the clinic is an attempt to achieve two goals. The first goal is to empower patients, family, and caregivers to be more informed and engaged in their own health and health care. The second goal is to enable healthcare providers to improve the ways they communicate with patients and support them better during and between office visits.

I hope this book is a step in “flipping the clinic” in the area of autonomic medicine.

The notion of flipping the clinic draws inspiration from Sal Khan, founder of the Khan Academy, the well-known not-for-profit organization that aims to offer “free world-class education” online, through an extensive library of videos and lectures as well as interactive challenges and assessments.

Khan Academy has sought to “flip” the classroom. Instead of listening to lectures in the classroom and doing “homework” at home, students listen to lectures at home and do “homework” in class, where the teacher can help students who are having difficulty. Students can also proceed at their own pace, mastering the material on their own schedule, not the teacher’s or the classroom’s.

- **Goals**
Power & responsibility of patients
Educate physicians & researchers
- **Internet-based medical education system**
- **Internet-based autonomic medical care system**
- **Dysautonomias as a prototype**
Applicable to other disorders of regulation

Ideas about “flipping the clinic” in the field of autonomic medicine

From a scientific point of view, flipping the clinic will be especially valuable for patients with multi-system disorders of regulation, such as dysautonomias. A system of education, lifestyle adjustments, support groups, and internet-based outcomes research can be compared with the standard medical practice models, in terms of both cost-efficiency and patient satisfaction.

Flipping the clinic applies similar principles to medical practice. I envision an internet-based, mutually educational system that is accessible by patients suffering from, students learning about, and practitioners managing autonomic disorders.

I hope this book is a step in that direction.

GLOSSARY

- ¹²³I-Metaiodobenzylguanidine (¹²³I-MIBG) *A particular type of radioactive drug that is used to visualize sympathetic nerves such as in the heart.*
- 3,4-Dihydroxyphenylacetaldehyde (DOPEGAL) *An intermediate metabolite of norepinephrine.*
- 3,4-Dihydroxyphenylacetic acid (DOPAC) *The main intra-neuronal metabolite of dopamine.*
- 3,4-Dihydroxyphenylglycol (DHPG) *The main intra-neuronal metabolite of norepinephrine.*
- 3-Methoxy-4-hydroxyphenylglycol (MHPG) *A major end-product in the metabolism of norepinephrine.*
- 5-Hydroxyindoleacetic acid (5-HIAA) *The main end-product in the metabolism of serotonin.*
- 5-Hydroxytryptophan (5-HTP) *The amino acid precursor of serotonin.*
- 6-[¹⁸F]Fluorodopamine (¹⁸F-Dopamine) *A drug that is the catecholamine, dopamine, with a fluorine atom attached that is a radioactive isotope called a positron emitter. Positron-emitting fluorodopamine is used to visualize sites of sympathetic innervation such as in the heart.*
- 6-[¹⁸F]Fluorodopa (¹⁸F-DOPA) *A drug that is the catechol amino acid, DOPA, with a fluorine atom attached that is a type of radioactive isotope called a positron emitter. Positron-emitting fluorodopa is used to visualize sites of dopaminergic innervation in the brain.*

-A-

AAD (Abbreviation for autoimmunity-associated autonomic denervation)

AAG (Abbreviation for autoimmune autonomic ganglionopathy)

Acetylcholine *A particular chemical that functions as the chemical messenger of the parasympathetic nervous system and the sympathetic cholinergic system. Acetylcholine is also the mediator of transmission in ganglia.*

ABPM *(Abbreviation for ambulatory blood pressure monitoring)*

Acetate *A small organic molecule that is a common building block in the body.*

Acetylcholinesterase (AChE) *An enzyme that rapidly breaks down acetylcholine in the extracellular fluid.*

Acetyl coenzyme A *A small organic molecule that is combined with choline to form the chemical messenger acetylcholine.*

ACE *(Abbreviation for angiotensin-converting enzyme)*

ACh *(Abbreviation for acetylcholine)*

AChE *(Abbreviation for acetylcholinesterase)*

Adenosine triphosphate (ATP) *The main source of chemical energy in the body.*

ADH *(Abbreviation for antidiuretic hormone)*

Adie's pupil *(also called Adie's tonic pupil) A condition in which a pupil is relatively large and constricts slowly in bright light.*

Adrenal, adrenal gland *A gland near the top of each kidney that produces hormones—steroids such as cortisol and catecholamines such as adrenaline.*

Adrenalectomized *Having the adrenal glands removed.*

Adrenaline *The same as epinephrine.*

Adrenal medulla *The “marrow,” or core, of the adrenal gland.*

Adrenergic *Referring to cells or neurons that use adrenaline or norepinephrine as chemical messengers.*

Adrenoceptors *Specialized proteins in cell membranes of various tissues that bind to the catecholamines norepinephrine (noradrenaline) or epinephrine*

(adrenaline), resulting in changes in the state of activity of the cells.

Adrenocortical *Referring to the adrenal cortex, the outer layer of the adrenal gland.*

Adrenomedullary hormonal system (AHS) *The part of the autonomic nervous system where epinephrine (adrenaline) is released from the adrenal medulla.*

AHS *Abbreviation for adrenomedullary hormonal system, synonymous with the sympathetic adrenergic system (SAS).*

AIDS *Abbreviation for acquired immunodeficiency syndrome, the final stage of HIV disease.*

¹³¹I-Albumin *Albumin that is tagged with a trace amount of radioactive iodine (¹³¹I). Injection of ¹³¹I-albumin is the basis for a test to measure the blood volume.*

Albumin *A prominent protein in the bloodstream.*

Alcohol dehydrogenase *An enzyme that breaks down alcohol.*

Aldehyde dehydrogenase (ALDH) *An enzyme involved in the intra-neuronal metabolism of dopamine.*

Aldehyde/aldose reductase (AR) *An enzyme that converts some aldehydes to glycols.*

Aldehyde *A type of chemical containing a CHO group. Aldehydes formed within cells are very reactive.*

ALDH (Abbreviation for aldehyde dehydrogenase) *ALDH is an important enzyme in the metabolism of dopamine in neurons.*

Aldosterone *The body's main sodium-retaining hormone. Aldosterone is steroid produced in the adrenal gland.*

Algorithm *A step by step procedure for solving a problem.*

Alizarin red *A pigment powder that turns purple when wet, used in sweat testing.*

Alkali *A base that dissolves in water and produces a pH more than 7.*

Allostasis A concept according to which goal values for internal variables can change as a function of circumstances.

Allostatic load Cumulative wear and tear from allostasis.

Alpha-adrenoceptor One of the two types of receptors for norepinephrine (noradrenaline) and epinephrine (adrenaline).

Alpha-1 adrenoceptors A particular type of adrenoceptors that are prominent in blood vessel walls. Stimulation of alpha-1 adrenoceptors in blood vessel walls causes the vessels to constrict.

Alpha-2 adrenoceptor blocker A drug that blocks alpha-2 adrenoceptors.

Alpha-2 adrenoceptors A type of adrenoceptor that is present on particular cells in the brain, in blood vessel walls, in several organs, and on sympathetic nerve terminals.

Alpha-methylDOPA (Aldomet™) A drug that resembles levodopa and is an effective drug to treat high blood pressure.

Alpha-synuclein A protein found in Lewy bodies and glial cytoplasmic inclusions.

Alzheimer's disease A common neurodegenerative disease causing dementia.

Amaurosis fugax Transient, painless loss of vision, usually due to a problem with blood flow to part of the brain.

Amphetamines Drugs that share a particular chemical structure that cause decreased appetite, increased attention, decreased sleep, and behavioral activation.

Amine A chemical containing a nitrogen atom with hydrogen atoms attached.

Amino acid A particular type of chemical that contains an amino chemical group and a carboxylic acid chemical

group and is a “building block” of proteins.

Amygdala A structure of the limbic system in the brain, involved with emotional responses.

Amyloidosis Any of a variety disorders in which a type of protein called amyloid is deposited within body organs.

Anaphylaxis A severe, rapidly developing allergic response.

Anemia A decreased amount of red blood cells. Anemic patients look pale and feel tired.

Angina pectoris An unpleasant squeezing or pressure sensation due to inadequate delivery of oxygenated blood to the heart muscle, such as from coronary artery disease.

Angiokeratomas Benign tumors of skin capillaries. Angiokeratomas are characteristic of Fabry disease.

Angiotensin II A particular peptide hormone that produces blood vessel constriction. Angiotensin II is a key part of the renin-angiotensin-aldosterone system.

Angiotensin-converting enzyme (ACE) An enzyme of the renin-angiotensin-aldosterone system that converts angiotensin I to angiotensin II.

Anhidrosis Lack of sweating.

Anoxia Absence of oxygen.

ANS (Abbreviation for autonomic nervous system)

Anterior cingulate cortex A part of the frontal lobe of the cerebral cortex, thought to play a role in the experience of emotions. The anterior cingulate has connections with both the “emotional” limbic system and the “cognitive” prefrontal cortex.

Antibody A large, Y-shaped protein produced mainly by plasma cells that is used by the immune system to identify and neutralize pathogens such as bacteria and viruses.

Anticipatory control A form of predictive or anticipatory regulation, largely synonymous with feed-forward

regulation.

Antidiuretic hormone (ADH) Same as vasopressin.

Anti-Hu An antibody produced in the setting of some cancers.

Apical The adjective for apex, or tip. The apical left ventricle is the tip of the heart.

Apnea Temporary cessation of breathing.

Aquaporins A group of membrane channels that transport water.

Arginine vasopressin (Synonymous with vasopressin)

Arachnodactyly A condition in which a person has long, thin fingers.

Arrector pili Small muscles that cause the hair to stand up.

Arrestins A family of chemicals that help turn off the intracellular cascade that activates cells when G-protein-coupled receptors such as beta-adrenoceptors are occupied.

Arrhythmia Abnormal rhythm, usually referring to abnormal heart rhythm.

Arterial baroreflex A rapid reflex that keeps arterial blood pressure within bounds. The reflex is evoked when the baroreceptors in arteries are stretched.

Arterial blood sampling Obtaining blood from a large blood vessel that moves blood away from the heart.

Arterial pressure The blood pressure in an artery.

Arteries Large blood vessels that carry blood from the heart.

Artery A large blood vessel that carries blood from the heart. Arteries (with the exception of the arteries to the lungs) carry oxygen-rich blood at high pressure.

Arteriole Tiny arteries that carry blood from the heart, like “twigs” of the arterial tree. The overall amount of constriction of arterioles is the main determinant of the total resistance to blood flow in the body. Constriction of

arterioles therefore increases the blood pressure, just like tightening the nozzle of a garden hose increases the pressure in the hose.

Arteriosclerosis Hardening of arteries.

Ascorbic acid (Synonymous with vitamin C)

Ashkenazi Referring to people of Eastern European Jewish ethnicity.

Aspartame A type of artificial sweetener. Aspartame is a methyl ester of aspartic acid/phenylalanine. Because it is broken down to form phenylalanine, patients with PKU should be aware that ingesting aspartame-sweetened foodstuffs can build up phenylalanine levels.

Asphyxiation Severe, sudden loss of oxygen supply due to lack of breathing, such as in suffocation.

Aspiration Inhalation of a foreign body into an airway.

Asthma A disease of the airways that involves episodes of airway spasm, producing wheezing, coughing, and shortness of breath.

Asystole A state of no electrical activity and therefore no pumping activity of the heart. Asystole is a cause of sudden death.

ATPase An enzyme that breaks down ATP, releasing energy.

Atropine A drug that blocks muscarinic acetylcholine receptors.

Auerbach's plexus A nerve network in the wall of the gastrointestinal tract, part of the enteric nervous system.

Autocrine/paracrine A type of arrangement where a chemical messenger acts on the same or nearby cells from the site of its release.

Autoimmune Referring to an abnormal immune response against substances or tissues in the body.

Autoimmune autonomic ganglionopathy (AAG) A rare form of

autonomic failure associated with high levels of antibodies to the neuronal nicotinic receptor, resulting in impaired transmission of autonomic nerve impulses in ganglia.

Autoimmune autonomic neuropathy *A form of autonomic failure associated with an “attack” of the immune system on a part of the autonomic nervous system.*

Autonomic *Referring to the autonomic nervous system.*

Autonomic dysreflexia *A condition after a spinal cord injury in which afferent stimulation, such as from filling of the urinary bladder, evokes a large increase in blood pressure.*

Autonomic function testing *Testing of one or more functions of the autonomic nervous system.*

Autonomic medicine *A medical discipline that focuses on clinical disorders of the autonomic nervous system.*

Autonomic myasthenia *Nickname for a form of chronic autonomic failure associated with an antibody to the acetylcholine receptor responsible for transmission of nerve impulses in ganglia.*

Autonomic nerve supply *The amount of autonomic nerve fibers and terminals in a tissue or organ.*

Autonomic nervous system (ANS) *The body’s “automatic” nervous system, responsible for many automatic, usually unconscious processes that keep the body going.*

Autonomically mediate syncope *Syncope due to alterations in activities of the components of the autonomic nervous system. A fainting reaction is an example of autonomically mediated syncope.*

Autosomal dominant *A situation where even one copy of the mutated gene is sufficient to produce the disease.*

Autosomal recessive *A situation where copies of the mutated gene on each chromosome produce the disease.*

Autotoxic *A characteristic of chemicals that harm the cells in*

which they are produced.

Autotoxicity A process by which a chemical harms the cells in which it is produced.

AVP (Abbreviation for arginine vasopressin)

Axon reflex A type of reflex where stimulation of nerves going towards the brain leads directly to a change in nerve activity towards a nearby site.

-B-

B cell (also known as B lymphocyte) A particular type of lymphocyte white blood cell. B cells secrete antibodies and also present antigen and secrete cytokines.

Baroreceptor reflex The same as baroreflex.

Baroreceptors Stretch or distortion receptors in the walls of large blood vessels such as the carotid artery and in the heart muscle.

Baroreflex A rapid reflex where an increase in blood pressure sensed by the brain leads to relaxation of blood vessels and a decrease in heart rate. The baroreflex keeps blood pressure stable.

Baroreflex failure A disorder in which the baroreceptor reflex fails, resulting in variable blood pressure and orthostatic intolerance.

Baroreflex-cardiovagal failure A situation where there is a lack of the normal change in the cardiac interbeat interval for a given change in systolic blood pressure.

Baroreflex-cardiovagal gain The change in cardiac interbeat interval for a given change in systolic blood pressure.

Baroreflex-sympathoneural failure A situation where there is a lack of the normal reflexive increase in sympathetic noradrenergic outflow for a given decrease in blood

pressure.

Baroreflex-sympathoneural gain *The change in sympathetic outflow for a given change in arterial blood pressure.*

Barostat *The conceptual homeostatic comparator that keeps the blood pressure stable.*

Basal *In describing the anatomy of the heart, referring to the upper part, nearest the “stem” of the great vessels, as opposed to apical, referring to the tip of the heart that one can palpate in the front of the chest.*

Basal ganglia *Structures in the brain that are below the cortex and above the brainstem.*

Basic *Having an alkaline pH.*

Beighton score *A scoring system for rating joint hyperextensibility.*

Benign prostatic hypertrophy (BPH) *Long-term enlargement of the prostate gland that does not result from a cancer.*

Benzodiazepine *A type of drug with a particular chemical structure that causes sedation, an anti-anxiety effect, relaxation of skeletal muscle, and decreased seizure activity.*

Beta-adrenoceptor *One of the two types of receptors for norepinephrine (noradrenaline) and epinephrine (adrenaline).*

Beta-1 adrenoceptors *One of the three types of beta-adrenoceptors, prominent in the heart muscle.*

Beta-2 adrenoceptors *One of the three types of beta-adrenoceptors, prominent in blood vessel walls in skeletal muscle, in the heart muscle, and on sympathetic nerve terminals.*

Beta-3 adrenoceptors *One of the three types of beta-adrenoceptors, prominent in fatty tissue.*

Beta-adrenoceptor blocker *A type of drug that blocks one or*

more types of beta-adrenoceptors.

Beta-Adrenoceptors *One of the two types of receptors for the norepinephrine (noradrenaline) and epinephrine (adrenaline).*

Bethanechol (Urecholine™) *A drug that stimulates some receptors for acetylcholine, mimicking the effects of stimulating the parasympathetic nervous system.*

Bicuspid aortic valve *A congenital abnormality in which the aortic valve has two rather than the normal three leaflets.*

Biomarker *An objective measure of a biological or disease process.*

Blood glucose *The concentration of the important metabolic fuel, glucose (dextrose), in the blood.*

Blood pressure *The pressure in arteries. Systolic blood pressure is the maximum pressure while the heart is beating, and diastolic blood pressure is the minimum pressure between heartbeats.*

Blood volume *The total volume of blood in the body. Most of the blood volume is in veins.*

Blood-brain barrier *A physical and chemical barrier that keeps compounds in the bloodstream from entering the substance of the brain.*

Botulinum toxin *A toxic chemical released from a particular bacterium. Botulinum toxin blocks release of acetylcholine.*

BPH (Abbreviation for benign prostatic hypertrophy)

Bradykinesia *Slow movement, especially slow initiation of movement.*

Brain fog *Decreased ability to concentrate, remember, or carry out executive functions.*

Brainstem *The lower part of the brain, located just above the spinal cord. The brainstem includes the hypothalamus, midbrain, pons, and, just at the top of the spinal cord, the*

medulla oblongata.

Bromocriptine *A drug that blocks a class of dopamine receptors. In post-partum women, injection of bromocriptine prevents lactation.*

Bronchioles *Small airway tubes in the lungs.*

Bruit *A whooshing sound that can be heard with a stethoscope, due to turbulent blood flow through an area of arterial narrowing.*

Buccal *Referring to the cheek.*

Buffering *In homeostatic systems theory, a process that diminishes the impact of an external disturbance on the level of a monitored variable.*

-C-

Cachexic *Having the appearance of wasting, as in end-stage cancer.*

Caffeic acid *A particular chemical found in coffee beans that is not caffeine.*

Caffeine *A chemical found in high concentrations in coffee beans.*

Carbidopa *A drug that inhibits the conversion of L-DOPA (levodopa) to dopamine. Carbidopa does not enter the brain from the bloodstream and blocks the conversion of L-DOPA to dopamine outside the brain.*

Cardiac output *The amount of blood pumped by the heart in one minute.*

Cardiac sympathetic neuroimaging *A clinical laboratory test designed to visualize the sympathetic innervation of the heart.*

Cardiovagal *Referring to effects of the vagus nerve on the heart (usually on the heart rate).*

Cardiovascular *Referring to the heart and blood vessels.*

Carotid arteries *The main arteries in the neck. In the upper neck, the common carotid artery splits into the external and internal carotid arteries.*

Carotid sinus *A region at the split of the common carotid artery into the internal and external carotid arteries. In humans, the carotid sinus contains distortion receptors called baroreceptors.*

Carotid sinus nerve *(Also called Hering's nerve) A branch of the glossopharyngeal nerve that carries nerve fibers from the carotid sinus and carotid body.*

Carotid sinus stimulation *A method to control high blood pressure using a device that electrically stimulates the carotid sinus.*

CASS *(Abbreviation for Composite Autonomic Severity Scale)*

Catechol-O-methyltransferase (COMT) *A major enzyme metabolizing catechols in non-neuronal cells.*

Catecholaldehyde *A chemical that contains both a catechol group and an aldehyde. DOPAL is a catecholaldehyde.*

Catecholaldehyde hypothesis *A concept in which aldehyde metabolites of catecholamines cause or contribute to neuronal death, such as in Parkinson's disease.*

Catecholamine autotoxicity *A concept in which spontaneous or enzyme-catalyzed oxidation of cytoplasmic catecholamines causes or contributes to neuronal death, such as in Parkinson's disease.*

Catecholamine *A member of an important chemical family that includes adrenaline.*

Catecholamines *Norepinephrine (noradrenaline) epinephrine (adrenaline), and dopamine.*

Catechol *A chemical that has a catechol structure in it. Dopamine, norepinephrine, adrenaline, and DOPA are*

catechols.

Catechols *Chemicals that have a particular structure in them called catechol. Dopamine, norepinephrine, adrenaline, and DOPA are catechols.*

Catechol-O-methyltransferase (COMT) *An enzyme that breaks down catechols in non-neuronal cells.*

Caudal ventrolateral medulla (CVLM) *A region in the lower, outer part of the medulla. The CVLM is part of the central autonomic network. Activation of neurons in the CVLM inhibits activities of neurons in the RVLM.*

Caudate *A brain structure that is part of the striatum, in the basal ganglia.*

Cell membrane norepinephrine transporter (NET) *The transporter responsible for “recycling” of norepinephrine back into sympathetic nerves.*

Cellcept (Mycophenolic acid) *A drug that inhibits part of the immune system.*

Central nervous system *The brain and spinal cord.*

Central Sympathetic Hyperactivity *A condition where there is an increase in the rate of sympathetic nerve traffic in the body as a whole.*

Cerebellar *Referring to the cerebellum.*

Cerebellar atrophy *A decrease in size of the cerebellum, a part of the brain.*

Cerebellum *A part of the brain, located above and behind the brainstem, that plays important roles in coordination of movement and the sense of orientation in space.*

Cerebrospinal fluid (CSF) *The clear fluid that bathes the brain and spinal cord.*

Cervical spinal cord *The spinal cord at the level of the neck.*

ChAT (Abbreviation for choline acetyltransferase) *ChAT catalyzes the production of acetylcholine from choline and*

acetyl coenzyme A.

Cheese effect *Side effects such as paroxysmal hypertension from eating tyramine-containing foodstuffs in the setting of monoamine oxidase inhibition.*

Chemoreflex *A reflex initiated by stimulation of chemical receptors, such as those in the carotid body, that respond to changes in blood concentrations of carbon dioxide, hydrogen ion, and oxygen.*

Chiari malformation *An anatomic abnormality where part of the brainstem falls below the hole between the brain and spinal cord.*

Chief Complaint *A single phrase or sentence that describes in the patient's own words what has been bothering the patient that has led to the patient coming in for evaluation.*

Choline *A small organic molecule that is used in the body to produce acetylcholine.*

Choline acetyltransferase (ChAT) *The enzyme that catalyzes the production of acetylcholine from choline and acetyl coenzyme A.*

Chorea *A type of quick abnormal movement of the hands or feet.*

Choroid plexus *A web-like network of cells in the brain that are the source of the cerebrospinal fluid.*

Chromosome *Organized structures of DNA in cells. Humans have 23 pairs of chromosomes, including 2 sex chromosomes (X and Y in males, 2 X chromosomes in women).*

Chronic autonomic failure *Long-term failure of the autonomic nervous system.*

Chronic fatigue syndrome *A condition where the patient has a sense of persistent fatigue for more than six months, without an identified cause.*

Chronic orthostatic intolerance *Long-term inability to tolerate standing up.*

Ciliary ganglion *A parasympathetic ganglion at the back of the eye socket.*

Classical conditioning *A form of association learning where two stimuli are repeatedly paired; a response that is at first elicited by the second stimulus (unconditioned stimulus) is eventually elicited by the first stimulus alone (conditioned stimulus). Classical conditioning is synonymous with Pavlovian conditioning.*

Clearance *The volume of fluid cleared of a substance in a given amount of time.*

Clonidine *A drug that stimulates alpha-2 adrenoceptors in the brain, in blood vessel walls, and on sympathetic nerve terminals. Clonidine decreases release of norepinephrine from sympathetic nerves and decreases the blood pressure.*

Clonidine suppression test *A test based on effects of clonidine administration on blood pressure and plasma levels of chemicals such as norepinephrine (noradrenaline).*

Coat hanger phenomenon *Pain in the back of the neck and shoulders during standing. This can be a symptom of chronic orthostatic intolerance.*

Cold pressor test *An autonomic function test in which the patient dunks a hand into a bucket of ice-cold water and keeps the hand immersed. Normally blood pressure increases in this situation.*

Common carotid artery *A large artery on each side of the neck that supplies blood to the head and neck.*

Common faint *The same as neurocardiogenic syncope, autonomically mediated syncope, and reflex syncope.*

COMPASS *(Abbreviation for Composite Autonomic Symptom Score) The “COMPASS 31” scale contains a total of 31*

questions in 6 domains, yielding an overall autonomic symptom score from 0 to 100. The domains are orthostatic intolerance (4 questions), vasomotor (3 questions), secretomotor (4 questions), pupillomotor (5 questions), bladder (3 questions), and gastrointestinal (including diarrhea, constipation, and gastroparesis, 12 questions).

Compensatory activation *A situation where failure of one effector system compensatorily activates another effector system, allowing a degree of control of a monitored variable.*

Complex 1 (NADH:ubiquinone oxidoreductase) *The first enzyme in the mitochondrial respiratory chain.*

Composite Autonomic Severity Scale (CASS) *A scale to rate the severity of autonomic failure.*

Composite Autonomic Symptom Score 31 (COMPASS 31) *An autonomic symptom scale that contains a total of 31 questions in 6 domains, yielding an overall autonomic symptom score from 0 to 100.*

COMT (Abbreviation for catechol-O-methyltransferase) *COMT is an important enzyme that breaks down catechols in non-neuronal cells.*

Conductance *A measure of how easily electricity flows along a particular path.*

Congenital *Present from birth.*

Congenital central hypoventilation syndrome (CCHS) *A rare inherited disease in which the patients do not have the normal reflexive respiratory responses.*

Congestive heart failure (CHF) *A condition in which the heart doesn't pump blood adequately and the blood backs up into the lungs.*

Conjunctival injection *Swollen blood vessels in the whites of the eyes, giving the appearance of being "blood shot."*

- Consilience** *Convergence of evidence from independent, unrelated sources that enables strong conclusions.*
- Constipation** *Infrequent and difficult bowel movements.*
- Contraction band necrosis** *A particular microscopic pathologic appearance of dead heart muscle that can result from high levels of adrenaline.*
- Conversion reaction** *Neurological symptoms such as numbness, blindness, or paralysis without an identified organic cause.*
- Core temperature** *The temperature at the core of your body, such as the temperature of the arterial blood.*
- Coronary arteries** *The arteries that deliver blood to the heart muscle.*
- Coronary artery disease** *A condition where the coronary arteries become narrowed or blocked by fatty deposits and thickening of the blood vessel walls.*
- Coronary ischemia** *Lack of adequate blood flow to heart muscle via the coronary arteries.*
- Corpora cavernosa** *A pair of sponge-like highly vascularized structures in the penis that when engorged with blood produces erection.*
- Corpus striatum** (synonymous with striatum) *The caudate and putamen in the basal ganglia of the brain.*
- CPAP** (Abbreviation for continuous positive airway pressure). *A method to treat sleep apnea by preventing airways from collapsing.*
- CPVT** (Abbreviation for catecholaminergic polymorphic ventricular tachycardia) *CPVT is a rare genetic disorder in which life-threatening abnormal heart rhythms can be evoked in response to elevated circulating levels of catecholamines.*
- Cranial nerves** *The twelve nerves that come through holes in the*

skull from the brainstem and go to many organs, from the eyes to the gastrointestinal tract.

Curare *A poison that paralyzes by blocking nicotinic acetylcholine receptors at neuromuscular junctions in skeletal muscle.*

CVLM *Abbreviation for caudal ventrolateral medulla, a part of the central autonomic network.*

Cybernetic Medicine (Synonymous with Scientific Integrative Medicine) *A conceptual framework for linking systems biology with integrative physiology in order to understand disease mechanisms. The concepts include (i) negative feedback regulation; (ii) homeostats; (iii) multiple effectors; (iv) effector sharing; (v) stress; (vi) distress; (vii) allostasis; and (viii) allostatic load.*

Cyclic adenosine monophosphate (cAMP) *A key chemical “second messenger” inside cells.*

Cytokines *Proteins that are secreted by cells of the immune system and exert effects on other cells. Examples of cytokines are interferons, interleukins, and tumor necrosis factors.*

Cytoplasm *The gel-like solution that fills cells.*

-D-

d-Amphetamine *The dextro- mirror image form of amphetamine.*

DA *(Abbreviation for dopamine)*

DAN *(Abbreviation for diabetic autonomic neuropathy)*

DAT *(Abbreviation for the cell membrane dopamine transporter)*

DAT scan *A type of scan of the brain that is used to detect loss of dopamine terminals in the striatum, as in Parkinson’s*

disease.

Desmopressin (DDAVP) *A synthetic form of vasopressin, the anti-diuretic hormone.*

DBH (Abbreviation for dopamine-beta-hydroxylase)

Dehydration *Abnormal lack of water in the body.*

Delayed orthostatic hypotension *A fall in the blood pressure after prolonged standing.*

Dementia with Lewy bodies (DLB, synonymous with Lewy body dementia, LBD) *A form of dementia in which the brain contains abundant Lewy bodies.*

Denervated *Having no nerves.*

Denervation supersensitivity *Increased sensitivity of a process as a result of loss of delivery of a chemical messenger to its receptors that normally mediate the process.*

Detrusor *A smooth muscle in the wall of the urinary bladder that causes the urinary bladder to contract.*

Dextro-amphetamine (Same as d-amphetamine)

DHPG (Abbreviation for 3,4-dihydroxyphenylglycol) *DHPG is the main intra-neuronal metabolite of norepinephrine.*

Diabetes *A disease state with excessive volume of urination and excessive water intake. Diabetes mellitus results from lack of insulin effects in the body. Diabetes insipidus results from lack of antidiuretic hormone (vasopressin) in the body.*

Diabetic autonomic neuropathy (DAN) *Dysautonomia in the setting of diabetes mellitus.*

Diagnosis *A decision about the cause of a specific case of disease.*

Dihydrocaffeic acid *A particular chemical that is a breakdown product of caffeic acid.*

Dihydropteridine reductase (DHPR) deficiency *A rare, atypical form of phenylketonuria (PKU).*

Dishabituation *A return to the initial magnitude of response after habituation has taken place.*

Distal *Further away from the center or point of attachment in the body.*

Distress *A form of stress that is consciously experienced, where the individual senses an inability to cope, attempts to avoid or escape the situation, evinces instinctively communicated signs, and has adrenal gland activation. Selye defined distress as stress that is unpleasant or damaging.*

DNA *A long molecule, in the shape of a double helix, that contains genetic instructions.*

DOPA (Abbreviation for 3,4-dihydroxyphenylalanine, levodopa) *DOPA, a catechol amino acid, is the precursor of the catecholamines.*

DOPA decarboxylase (DDC, LAAAD) *The enzyme responsible for conversion of L-DOPA to dopamine in the body.*

DOPA-responsive dystonia *A neurological disease resulting from decreased activity of an enzyme required for synthesizing tetrahydrobiopterin.*

DOPAC (Abbreviation for 3,4-dihydroxyphenylacetic acid) *DOPAC is the main intra-neuronal metabolite of dopamine.*

DOPAL (Abbreviation for 3,4-dihydroxyphenylacetaldehyde) *DOPAL is the catecholaldehyde metabolite of dopamine.*

Dopamine *One of the body's three catecholamines. Dopamine deficiency in the striatum causes the movement disorder in Parkinson's disease.*

Dopamine sulfate *A particular metabolite of dopamine.*

Dopamine-beta-hydroxylase (DBH) *The enzyme responsible for conversion of dopamine to norepinephrine in the body.*

Dopamine-beta-hydroxylase deficiency *A rare cause of neurogenic orthostatic hypotension, due to lack of the*

enzyme required for producing norepinephrine from dopamine.

DOPET *(Abbreviation for 3,4-dihydroxyphenylethanol)*

DOPET is a minor metabolite of dopamine.

Dorsal *Referring to the back part.*

Dorsal motor nucleus *The nucleus of the vagus nerve in the back of the medulla of the brainstem.*

Dorsal root ganglion *A particular cluster of nerve cell bodies in a posterior root of a spinal nerve. The neurons receive input from sense organs and project to the spinal cord.*

Dorsomedial *Toward the back and central. The dorsomedial medulla contains the nucleus of the solitary tract.*

Droxidopa *Synonymous with L-DOPS, L-threo-dihydroxyphenylserine, and Northera™. Droxidopa is converted in the body to norepinephrine.*

Dysautonomia *A condition in which a change in the function of one or more components of the autonomic nervous system adversely affects health.*

Dysautonomias *Conditions in which a change in the function of one or more components of the autonomic nervous system adversely affects health.*

Dysphoria *Sour mood; a state of unease or generalized dissatisfaction with life.*

Dyspnea *Shortness of breath.*

-E-

Eaton-Lambert syndrome *A rare autoimmune condition in which there is decreased acetylcholine release at neuromuscular junctions, resulting in weakness.*

Edinger-Westphal nucleus *A cluster of nerve cells in the midbrain from which parasympathetic nerves travel to the*

eye.

Edrophonium (*brand name Tensilon™*) *A drug that rapidly, temporarily blocks acetylcholinesterase.*

EDS (*Abbreviation for Ehlers-Danlos syndrome*)

Effector *An entity that influences the level of a monitored variable. The sympathetic noradrenergic system is an example of an effector for controlling the blood pressure.*

Effector sharing *A situation in which two homeostats use the same effector.*

Ehlers-Danlos syndrome *A type of inherited disease of structural tissue that involves the protein, collagen. Some signs of Ehlers-Danlos syndrome are stretchy skin and overly flexible joints.*

Endothelial *Referring to the innermost layer in a blood vessel wall.*

Endothelial cells *Cells that make up the innermost wall of blood vessels.*

Enkephalins *A class of compounds made in the body that bind to opiate receptors.*

Enophthalmos *A posterior displacement of the eyeball within the orbit.*

ENS (*Abbreviation for enteric nervous system*) *The ENS component of the autonomic nervous system found in the walls of the gastrointestinal tract.*

Enteric nervous system (ENS) *A component of the autonomic nervous system found in the walls of the gastrointestinal tract.*

Enzyme *A type of protein that accelerates a biochemical process.*

Ephedrine *A particular drug that acts in the body as a sympathomimetic amine.*

Epinephrine (adrenaline) *The main hormone released from the*

adrenal medulla. Epinephrine is one of the body's three catecholamines.

EPI (Abbreviation for epinephrine) EPI is the main hormone released from the adrenal medulla.

Erectile failure Impotence from failure to have or sustain erection of the penis.

Ergotamine A particular drug that constricts blood vessels.

Ergotropic W.R. Hess's term referring to particular behaviors evoked by hypothalamic stimulation that seem to be directed outwards towards the environment.

Error control regulation Reflexive regulation via negative feedback in a homeostatic system.

Erythromelalgia A condition in which the patients complain of burning pain in the skin.

Erythropoietin A hormone that stimulates the bone marrow to produce red blood cells.

ETS (Abbreviation for endoscopic thoracic sympathectomy)

Eustress Selye's term for stress that is not harmful.

Exocytosis Release of the contents of vesicles into the extracellular fluid, after fusion and poration of the vesicles with the cell membrane.

Extracellular fluid (ECF) The fluid outside cells of the body. The ECF is composed of the interstitial fluid and the blood plasma.

Extravasation Leakage of fluid from blood vessels into the surrounding tissues.

-F-

Fabry disease A lipid storage disease due to deficiency of the enzyme alpha-galactosidase-A. The disease is manifested by angiokeratomas and anhidrosis.

Factitious *Falsification of symptoms without secondary gain.*

Fainting *Relatively rapid loss of consciousness that is not caused by heart disease.*

False-positive test *A positive test result when the patient does not actually have the disease.*

Familial Dysautonomia (FD) *A rare inherited disease that features abnormalities in sensation and in functions of the autonomic nervous system.*

FAC *(Abbreviation for familial amyloid cardiomyopathy)*

FAP *(Abbreviation for familial autonomic polyneuropathy)*

FBF *(Abbreviation for forearm blood flow)*

FD *(Abbreviation for Familial Dysautonomia) FD is a rare inherited disease that features abnormalities in sensation and in functions of the autonomic nervous system.*

F-DOPA *Fluorinated DOPA. ¹⁸F-DOPA is used to image the striatum in the brain by PET scanning.*

Feed-forward regulation *A form of predictive or anticipatory regulation, largely synonymous with anticipatory control.*

Fenfluramine *A particular drug that acts in parts of the nervous system where serotonin is the chemical messenger.*

Fibromyalgia *A condition that involves widespread, chronic pain and tenderness of muscle or connective tissues.*

First messenger *A hormone or other chemical messenger that acts on receptors on target cells. Second messengers within the target cells mediate the changes in cell functions.*

Flipping the clinic *A term referring to empowerment and responsibility of people in their medical care.*

Florinef™ *(Brand name for fludrocortisone)*

Fludrocortisone (Florinef™) *A type of artificial salt-retaining steroid drug.*

Fluorodopamine *A drug that is the catecholamine, dopamine,*

with a fluorine atom attached. The fluorine atom is a type of radioactive isotope called a positron emitter. Positron-emitting fluorodopamine is used to visualize sympathetic nerves such as in the heart.

Forearm blood flow (FBF) *The rate of inflow of blood into the forearm, usually expressed in terms of blood delivery per 100 cc of tissue volume per minute.*

Forearm vascular resistance (FVR) *The extent of resistance to blood flow in the forearm blood vessels.*

Free fatty acids *Chemicals that are breakdown products of triglycerides. Free fatty acids can be used as an energy source in some organs.*

Fungiform papillae *Particular taste buds on the tongue.*

FVR *(Abbreviation for forearm vascular resistance)*

-G-

G-protein *A particular type of protein (guanine nucleotide-binding-protein) that mediates the effects of receptor occupation.*

G-protein coupled receptor kinases (GRKs) *A class of enzymes that are activated by G-proteins.*

Galvanic skin response (GSR) *A physiological change in the amount of sweat, an index of ability of the skin to conduct electricity.*

Ganglia *Plural of ganglion.*

Ganglion *A clump of cells where autonomic nerve impulses are relayed between the spinal cord and target organs such as the heart.*

Ganglion blocker *A type of drug that inhibits the transmission of nerve impulses in ganglia.*

Gastroesophageal reflux *A condition in which stomach*

contents and acid go backward up the swallowing tube, the esophagus.

Gastroparesis *Poor stomach motility, so that food does not pass through the stomach properly.*

Gaucher disease *An inherited disease in which mutation of a enzyme called glucocerebrosidase causes accumulation of a type of fat called glucocerebroside in body organs.*

GCI *(Abbreviation for glial cytoplasmic inclusion)*

GDNF *(Abbreviation for glial cell line-derived neurotrophic factor)*

Gene *A segment of DNA that directs development and behavior in an organism. If the genetic material were an encyclopedia, the genes would be sentences.*

General Adaptation Syndrome (GAS) *Selye's concept of a unitary stress response proceeding in three stages—alarm, resistance, and exhaustion.*

Glands *Body structures that release chemicals.*

Glial cell *A type of non-neuronal “helper” cell in the brain.*

Glial cell line-derived neurotrophic factor (GDNF) *A nerve growth factor produced by glial cells.*

Glial cytoplasmic inclusions (GCIs) *Inclusion bodies in the cytoplasm of glial cells.*

Glomerulus *A microscopic tuft of arterioles that filters the plasma in the kidneys.*

Glomeruli *Plural of glomerulus. The glomeruli in the kidney filter the plasma.*

Glomerular filtrate *The fluid in kidney tubules after filtration of the plasma in the glomeruli.*

Glossopharyngeal nerve *The ninth cranial nerve.*

Glucagon *A hormone that plays a major role in regulation of glucose levels.*

Glucocerebrosidase *A particular enzyme. Mutation of the gene*

encoding glucocerebrosidase (GBA) causes Gaucher disease.

Glucocorticoid *A type of steroid made in the adrenal cortex that increases glucose levels.*

Glucose *One of the body's main fuels. The same as dextrose.*

Glucostat *The conceptual homeostatic comparator that keeps the blood glucose level stable.*

Glycogen *A multibranched polysaccharide of glucose that serves as a form of energy storage.*

Glycopyrrolate *A particular anti-cholinergic drug that is a muscarinic cholinergic antagonist.*

Good regulator *According to Ashby's good regulator theorem, a good regulator models well the system it regulates—like a good key models its lock. A good regulator is maximally efficient and simple: each value of the regulator corresponds to one and only one value of the regulated variable.*

Grinch syndrome *A reference to the Dr. Seuss character who had a heart that was “two sizes too small.” It has been proposed that marked tachycardia during orthostasis in Grinch syndrome patients is a compensation for low stroke volume.*

Growth hormone *A hormone released by the pituitary gland that promotes growth.*

GSR (Abbreviation for galvanic skin response) *A rapid increase in electrical conduction in the skin as a result of an increase in production of sweat.*

GTP cyclohydrolase (GTPCH) *An enzyme in the biosynthesis of tetrahydrobiopterin.*

GTPCH (Abbreviation for GTP cyclohydrolase)

Guillain-Barré syndrome *A condition involving autoimmune attack on neurons of the peripheral nervous system.*

Gustatory *Referring to tasting something.*

-H-

Habituation *The process by which repetition of a stimulus diminishes the physiological or emotional response.*

Heart block *An impediment to conduction of impulses in the electrical conduction pathways of the heart.*

Heart failure *A condition where the heart fails to pump an amount of blood for the tissues of the body.*

Hematocrit *The percent of the blood volume that is the volume of the red blood cells.*

Hemorrhage *Rapid blood loss from the circulation.*

Hereditary sensory and autonomic neuropathy type III (HSAN III) *(Synonymous with Familial Dysautonomia)*

Hereditary sensory and autonomic neuropathy type IV (HSAN IV) *A rare form of inherited disease involving lack of ability to sense pain and lack of sweating.*

Hereditary transthyretin amyloidosis *A rare but clinically and scientifically important cause of chronic autonomic failure.*

Heroin *A type of opiate drug.*

Heterozygous *A situation in which a genetic mutation is found on one chromosome but not the other.*

5-HIAA *(Abbreviation for 5-hydroxyindoleacetic acid) 5-HIAA is the main breakdown product of serotonin.*

5-hydroxyindoleacetic acid (5-HIAA) *The main breakdown product of serotonin.*

Hirschsprung's disease *A disease of newborns in which there is failure to pass meconium or stool due to a loss of enteric ganglion neurons.*

Histamine flare reaction *A particular appearance of the skin after local injection of histamine.*

History of the Present Illness (HPI) *A narrative history of a medical condition. The HPI is a key part of the medical history.*

HIV disease *A disease caused by the human immunodeficiency virus. The final stage of HIV disease is AIDS (acquired immunodeficiency syndrome), in which there is progressive failure of the immune system, setting the stage for certain life-threatening infections and cancers.*

Holmes-Adie syndrome *A condition in which there is Adie's pupil combined with a loss deep tendon reflexes.*

Homeostasis *A condition in which levels of monitored variables of the body are kept within bounds. Walter B. Cannon invented the word, "homeostasis," to describe the stability of various constituents of body fluids and of core temperature.*

Homeostat *A general term for a metaphorical physiological comparator. Information reaching the brain about the status of a monitored variable is compared with settings in the brain, and when there is a sensed discrepancy between what is sensed and what is set, this leads to altered activities of effectors that reduce the discrepancy. Homeostats are metaphors, as there are no known actual physiological comparators in the body. The "homeostat" also was a machine invented by W. Ross Ashby.*

Homovanillic acid (HVA) *The main end-product of dopamine metabolism.*

Homozygous *A situation in which the same genetic mutation is found on both chromosomes*

Hormone *A chemical released into the bloodstream that acts at remote sites in the body.*

- Horner's syndrome** *A syndrome of lid lag (ptosis), constricted pupil (miosis), and decreased sweating (anhidrosis) due to disruption of sympathetic nerve traffic.*
- HPA** *(Abbreviation for hypothalamic-pituitary-adrenocortical)*
The HPA axis plays an important role in distress and immunity.
- HPI** *(Abbreviation for history of the present illness, a key part of the medical history)*
- HR** *(Abbreviation for heart rate)*
- HSAN** *(Abbreviation for hereditary sensory and autonomic neuropathy)*
- Huntington's disease** *An inherited, progressive neurodegenerative disease of adults that involves involuntary limb movements and dementia.*
- HVA** *(Abbreviation for homovanillic acid)* *HVA is the main end-product of dopamine metabolism.*
- Hyperadrenergic orthostatic intolerance** *A condition where an inability to tolerate standing up is combined with signs or symptoms of excessive levels of catecholamines such as epinephrine (adrenaline).*
- Hypercarbia** *An excessive increase in the blood concentration of carbon dioxide.*
- Hyperdynamic circulation syndrome** *A condition where the rate and force of the heartbeat are abnormally increased.*
- Hyperglycemia** *A condition in which there is a high blood glucose level.*
- Hyperhidrosis** *A condition in which there is excessive sweating.*
- Hypernoradrenergic hypertension** *Long-term high blood pressure associated with increased release of norepinephrine from sympathetic nerves.*
- Hypertension** *A condition where the blood pressure is persistently increased.*

Hypertrophied *Characterized by an increase in the volume of an organ or tissue, due to enlargement of the component cells.*

Hypertrophy *An increase in the volume of an organ or tissue, due to enlargement of the component cells.*

Hypoglycemia *A condition where there is an abnormally low blood glucose level.*

Hypoglycemia unawareness *Failure of hypoglycemia to trigger epinephrine secretion and therefore symptoms of hypoglycemia.*

Hypothalamus *A region of the brain above the brainstem that is part of the limbic system.*

Hypothermia *A condition where there is an abnormally low body temperature.*

Hypoxia *Oxygen deficiency.*

-I-

IBS *(Abbreviation for irritable bowel syndrome)*

Idiopathic hyperhidrosis *Excessive sweating that has no known cause.*

IgE *An immunoglobulin that plays a key role in acute allergic reactions.*

IkappaB kinase-associated protein (IKAP) *The protein product encoded by the gene, IKBKAP. FD patients have decreased levels of this protein in nervous system tissue.*

IKBKAP *A particular gene, a type of mutation of which causes Familial Dysautonomia.*

ILBD *(Abbreviation for incidental Lewy body disease) ILBD is thought to be a form of pre-symptomatic Parkinson's disease.*

Imidazoline *A particular chemical structure*

- Immunoglobulin** *A type of glycoprotein produced by immune cells that acts as an antibody.*
- Impedance plethysmography** *A non-invasive medical test that measures small changes in electrical resistance. Impedance plethysmography can be used to measure changes in local blood flow.*
- Impotence** *Inability to have erection of the penis or ejaculation of semen.*
- Ileus** *Distention of the bowel due to lack of propulsive movement of contents.*
- Inappropriate sinus tachycardia** *Fast heart rate because of too rapid firing of the heart's pacemaker in the sinus node.*
- Incidental Lewy body disease (ILBD)** *The occurrence of Lewy bodies found at autopsy in clinically healthy people. ILBD is thought to be a form of pre-symptomatic Parkinson's disease.*
- Incontinence** *Sudden involuntary urination or bowel movement.*
- Inderal™** *(Brand name of propranolol)*
- Indirectly acting sympathomimetic amine** *A type of drug that produces effects similar to those of stimulating sympathetic nerves.*
- Innervation** *Nerve supply.*
- Instrumental conditioning** *A type of learning in which the organism's behavior is shaped based on the likelihood of reinforcement. Instrumental and operant conditioning are virtually synonymous. Operant conditioning refers to learning where behavior is controlled by consequences.*
- Insular cortex** *(also called the insula and insular lobe) A part of the cerebral cortex folded deep within the fissure separating the temporal lobe from the parietal and frontal lobes. The insular cortex is part of the central autonomic network.*

Insulin *An important hormone released from the pancreas that helps to control the blood glucose level.*

Insulin neuritis *A form of acute painful neuropathy due to rapid improvement in glucose levels by insulin treatment in the setting of long-term high glucose levels.*

Intermediolateral columns *The middle outer part of the spinal cord that contains sympathetic pre-ganglionic neurons.*

Interoceptive *Referring to input from sensors within body organs (especially the gut).*

Intima *The innermost layer of a blood vessel wall.*

Intravenous *Inside a vein. Drugs can be infused or blood sampled through an intravenous catheter.*

Intravenous saline *Physiological salt-in-water solution that is given by vein.*

Ionotropic *Referring to movement of ions across the cell membrane.*

Iontophoresis *A way of using electricity to deliver a drug to the skin surface.*

Isoproterenol (Isuprel™) *A particular drug that stimulates beta-adrenoceptors.*

Isoproterenol infusion test *A test where isoproterenol is given by vein, to see if this affects the ability to tolerate tilting or to measure the body's responses to stimulation of beta-adrenoceptors.*

Isuprel™ *The brand name of isoproterenol.*

IV *(Abbreviation for intravenous)*

IVIG *(Abbreviation for intravenous immunoglobulin)*

-J-

Juxtaglomerular apparatus *A specialized structure near the glomeruli of the kidneys that is involved with regulating*

renal blood flow and the rate of glomerular filtration.

-K-

Kinky hair disease *The same as Menkes disease.*

Klinefelter syndrome *A genetic disorder in which the genotype is XXY. People with Klinefelter syndrome phenotypically are men, because they have a Y chromosome, but they are feminized because they have two XX chromosomes.*

-L-

LAAAD *(Abbreviation for L-aromatic-amino-acid decarboxylase)*

L-aromatic-amino-acid decarboxylase (LAAAD) *The enzyme that converts levodopa to dopamine in the body.*

L-dihydroxyphenylalanine (Levodopa, L-DOPA) *L-dihydroxyphenylalanine is the precursor of the catecholamines in the body.*

L-Dihydroxyphenylserine (L-DOPS) *A particular amino acid that is converted to norepinephrine by the action of L-aromatic-amino-acid decarboxylase.*

L-DOPA *(Abbreviation for L-dihydroxyphenylalanine, the same as levodopa) L-DOPA is the precursor of the catecholamines in the body.*

L-DOPS *(Abbreviation for L-dihydroxyphenylserine, brand name Northera™) L-DOPS is turned into norepinephrine in the body.*

Lacrimal glands *Glands that produce tears.*

Lacrimation *Secretion of tears.*

Lambert-Eaton myasthenic syndrome *(Same as Eaton-Lambert syndrome) A neuromuscular disease resulting from*

autoimmunity to calcium channels.

Lesion *A damaging abnormality in a tissue.*

Levodopa *The same as L-DOPA and L-dihydroxyphenylalanine.*

Lewy body *A type of inclusion body in the cytoplasm of neurons. Lewy bodies contain abundant precipitated alpha-synuclein.*

Lewy body dementia (LBD; synonymous with dementia with Lewy bodies)

Lewy body diseases *A group of diseases characterized by Lewy bodies. The autonomic synucleinopathies Parkinson's disease with orthostatic hypotension and pure autonomic failure are examples.*

Limbic system *A group of brain structures above the level of the brainstem and below the level of the cerebral cortex.*

Locus ceruleus (LC) *A cluster of nerve cells in the pons of the brainstem. The LC is the main source of norepinephrine in the brain.*

Low pressure baroreceptors *Distortion receptors in the walls of the atria of the heart and great veins.*

LRRK2 (Abbreviation for leucine-rich repeat kinase 2) *A particular enzyme. Mutation of the gene encoding LRRK2 is a cause of familial Parkinson's disease.*

Lumbar puncture *A procedure where a needle is inserted into the lower back, such as to sample cerebrospinal fluid.*

Lymphocytes *A family of white blood cells that play important roles in immunity.*

-M-

Ma huang *Chinese name for an herbal remedy that is ephedrine.*

MACS (Abbreviation for Mast Cell Activation Syndrome)

- Macula densa** *An area of specialized cells in the juxtaglomerular apparatus that are sensitive to sodium chloride.*
- Malingering** *Falsification of symptoms with secondary gain.*
- MAO** *(Abbreviation for monoamine oxidase)*
- MAO-A and MAO-B** *(Abbreviations for monoamine oxidase-A and monoamine oxidase-B)*
- MAP** *(Abbreviation for mean arterial pressure)*
- Marfanoid** *Having the characteristics of being tall and thin, with long arms and legs and thin fingers.*
- Mast cell** *A particular type of immune cell that plays a role in rapid immune responses.*
- Mast Cell Activation Syndrome (MACS)** *A condition in which mast cells are activated inappropriately or excessively.*
- MAST** *(Abbreviation for military anti-shock trousers)*
- Mean arterial pressure (MAP)** *The average blood pressure in the arteries.*
- Meconium** *The earliest stool of a newborn.*
- Meissner's plexus** *A network of neurons in the submucosal layer of the wall of the small intestine.*
- Melanin** *A black pigment formed from oxidation of tyrosine or catechols.*
- Menkes disease** *A rare inherited disease of copper metabolism that causes death in early childhood.*
- Mesolimbic** *Referring to a nervous pathway from the midbrain to the limbic system.*
- Metaboreflex** *A type of chemoreflex where chemicals produced during exercise stimulate reflexive changes in autonomic outflows, resulting in increased oxygen delivery to the active skeletal muscle.*
- Metabotropic receptor** *A type of membrane receptor that acts through a second messenger. The muscarinic cholinergic*

receptor is an example of a metabotropic receptor.

Metanephrine (MN) *The O-methylated metabolite of epinephrine.*

Metanephrines *A general term for the O-methylated metabolite of norepinephrine, which is normetanephrine (NMN) and the O-methylated metabolite of epinephrine, which is metanephrine (MN).*

3-Methoxytyramine *The O-methylated metabolite of dopamine.*

3-Methoxytyrosine *The O-methylated metabolite of DOPA.*

Methylphenidate (Ritalin™) *A particular drug in the family of amphetamines.*

Metoclopramide *A drug that is an antagonist at dopamine receptors. Metoclopramide is used clinically to treat gastroesophageal reflux and delayed gastric emptying (gastroparesis).*

MHPG (Abbreviation for 3-methoxy-4-hydroxyphenylglycol).
MHPG is a major end-product of norepinephrine metabolism.

MIBG (Abbreviation for metaiodobenzylguanidine) ¹²³I-MIBG
is used for cardiac sympathetic neuroimaging.

Midodrine (Proamatine™) *A particular drug that can be taken as a pill and constricts blood vessels by way of stimulation of alpha-adrenoceptors, used commonly in the treatment of orthostatic hypotension and orthostatic intolerance.*

Milieu intérieur *Claude Bernard's concept of the fluid environment of nearly constant composition that bathes and nourishes the cells of the body.*

Military anti-shock trousers (MAST) suit *A type of inflatable trousers that decreases pooling of blood in the legs.*

Mineralocorticoid *A type of steroid that causes the body to retain sodium.*

Miosis *Constriction of the pupil.*

Mitochondria *Organelles within cells that produce chemical energy.*

mmHg *Abbreviation for millimeters of mercury, a measure of pressure.*

Monitored variable *A biological activity that can be sensed and the level of which can be controlled by effectors. Blood pressure, core temperature, and serum glucose levels are examples of monitored variables.*

Monoamine *A type of biochemical that contains a component called an amine group. Serotonin, norepinephrine, dopamine, and adrenaline are monoamines.*

Monoamine oxidase *An enzyme localized to the outer mitochondrial membrane that metabolizes catecholamines and related chemicals.*

Moxonidine *A particular drug that decreases blood pressure by decreasing sympathetic nerve traffic.*

MSA (Abbreviation for multiple system atrophy) *MSA is a rare progressive disease of the brain.*

MSA-C (Abbreviation for the cerebellar form of multiple system atrophy)

MSA-P (Abbreviation for the parkinsonian form of multiple system atrophy)

MSNA (Abbreviation for muscle sympathetic nerve activity)

Multiple system atrophy (MSA) *A rare progressive disease of the brain that includes failure of the autonomic nervous system.*

Muscarine *A chemical found in some mushrooms that stimulates muscarinic cholinergic receptors.*

Muscarinic *Referring to one of the two types of acetylcholine receptors. The other is nicotinic.*

Muscle sympathetic nerve activity (MSNA) *Pulse-synchronous traffic in sympathetic post-ganglionic fibers in peripheral*

nerves.

Mutation *A rare genetic change, like a “typo” in the genetic encyclopedia.*

Myasthenia gravis *An autoimmune disease usually associated with circulating antibodies to the skeletal muscle nicotinic receptor.*

Mydriasis *Dilation of the pupil.*

Myelin *A fatty, electrically insulating material found in sheaths surrounding nerve fibers.*

Myelinated *Having a myelin sheath.*

Myocardium *Muscle tissue of the heart.*

Myocytolysis *A microscopic pathologic finding in the heart that can reflect death of heart muscle cells due to exposure to catecholamines.*

-N-

NAD⁺ *(Abbreviation for the oxidized form of nicotinamide adenine dinucleotide) A type of co-enzyme required for some enzymes to function. NAD⁺ is an oxidizing agent that accepts electrons.*

nAChR *(Abbreviation for nicotinic acetylcholine receptor)*

NE *(Abbreviation for norepinephrine) NE is one of the body’s three catecholamines.*

Negative feedback *A situation where the output from a system is fed back into the system. Negative feedback reduces fluctuations in the output.*

Negative feedback loop *A type of control system in which alteration in the input about a monitored variable leads to an opposing alteration in the output via an effector. If the overall feedback of the system is negative, then the level of the monitored variable will tend to be stable. A*

thermostatic system is an example of a negative feedback loop. When the room temperature goes down, this leads to the furnace being turned on, which brings the room temperature back up.

Nerve growth factor (NGF) *A particular factor that is trophic for sympathetic nerves and dorsal root ganglion cells.*

Nerve terminal *The end of a nerve fiber, from which chemical messengers are released.*

Nerve traffic *Electrical signals conducted within a nerve.*

NET (Abbreviation for the cell membrane norepinephrine transporter)

NET deficiency *A rare cause of orthostatic intolerance resulting from decreased activity of the cell membrane norepinephrine transporter.*

Neurally mediated hypotension (NMH) *A sudden fall in blood pressure during provocative tilt table testing.*

Neurally mediated syncope *A condition that includes sudden loss of consciousness from a change in the function of the autonomic nervous system.*

Neurasthenia (Same as neurocirculatory asthenia) *A condition closely related to chronic fatigue syndrome that features exercise intolerance without identified cause, described mainly in medical literature from the former Soviet Union.*

Neurocardiogenic syncope (Same as Neurally Mediated Syncope and Autonomically Mediated Syncope).

Neurochemical *A chemical released from nervous tissue.*

Neurocirculatory asthenia *A condition closely related to chronic fatigue syndrome that features exercise intolerance without identified cause, described mainly in medical literature from the former Soviet Union.*

Neurodegeneration *Progressive loss of structure or function of neurons.*

Neuroendocrine system *A type of system in which chemical messengers released from nerve terminals act on cells that in turn release hormones into the bloodstream.*

Neurogenic orthostatic hypotension *A form of orthostatic hypotension (fall in blood pressure when the patient is upright) due to failure of reflexive release of norepinephrine in response to a decrease in venous return to the heart.*

Neuroimaging tests *Tests based on visualizing the nervous system.*

Neuroleptic *A type of tranquilizer drug, used to treat schizophrenia or other psychiatric conditions.*

Neuromelanin *A dark pigment in the cytoplasm of catecholaminergic neurons.*

Neuronal nicotinic receptor (nAChR) *The form of acetylcholine receptor that mediates ganglionic neurotransmission.*

Neuroimmunology *An inter-disciplinary field of medical science that focuses on interactions between the nervous system (including the autonomic nervous system) and the immune system (including cytokines).*

Neuropathic POTS *A form of postural tachycardia syndrome (POTS) thought to result from local or patchy loss of sympathetic nerves.*

Neuropathy *An abnormality of one or more peripheral nerves.*

Neuropharmacologic *A type of drug effect that acts on nervous tissue or mimics chemicals released in nervous tissue.*

Neurotransmitter *A chemical released from nerve fibers or terminals that produces effects on nearby cells.*

Nicotine *A chemical in tobacco that stimulates a particular type of receptor for the chemical messenger acetylcholine.*

Nicotinic *Referring to one of the two types of receptors for the*

chemical messenger acetylcholine. The other is muscarinic.

Nigrostriatal system *A dopaminergic network involving the substantia nigra of the midbrain and the striatum in the basal ganglia.*

Nitric oxide *A gas produced in the body that acts as a vascular relaxing factor.*

Nitroglycerine *A particular drug that relaxes walls of veins in the body.*

NMH *(Abbreviation for neurally mediated hypotension)*

Non-dipping *Absence of the normal nocturnal decrease in blood pressure.*

Non-myelinated *Lacking a myelin sheath.*

Non-selective beta-adrenoceptor blockers *A type of drug that blocks all types of beta-adrenoceptors.*

Noradrenergic *Referring to norepinephrine. Noradrenergic neurons use norepinephrine as their chemical messenger.*

Norepinephrine (noradrenaline) *The main chemical messenger of the sympathetic nervous system that is responsible for much of regulation of the cardiovascular system by the brain. Norepinephrine is one of the body's three catecholamines.*

Normal saline *A dilute solution of sodium chloride (table salt) that has the same concentration as in the serum.*

Normetanephrine (NMN) *The O-methylated metabolite of norepinephrine.*

NTRK1 *(Abbreviation for neurotrophic tyrosine kinase receptor type 1) Mutation of the gene encoding NTRK1 is a cause of type IV hereditary sensory and autonomic neuropathy.*

NTS *(Abbreviation for nucleus of the solitary tract) The NTS is the brainstem site of the initial synapse in the arterial*

baroreflex and other autonomic reflexes.

Nucleus of the solitary tract (NTS) *The brainstem site of the initial synapse in the arterial baroreflex and other autonomic reflexes. The NTS receives much of the afferent information from the viscera.*

Nucleus accumbens *A region at the bottom of the brain in front of the pre-optic area of the hypothalamus. The nucleus accumbens and the olfactory tubercle together form the ventral striatum, part of the basal ganglia. The nucleus accumbens is thought to play important roles in motivation, pleasure, reward, reinforcement learning, and addiction. It is part of the central autonomic network.*

-O-

Oculogyric crisis *A reaction to certain drugs or medical conditions in which there is prolonged, involuntary upward deviation of the eyes.*

OH *(Abbreviation for orthostatic hypotension) OH is a fall in blood pressure during standing.*

O-methylated *Having an O-methyl (methoxy) group, OCH₃. This is a characteristic of common breakdown products of catecholamines, such as homovanillic acid.*

Ondine's curse *A term used to refer to congenital central hypoventilation syndrome.*

Ontogenetic *Referring to the development of an organism from egg fertilization through the lifespan.*

Operant conditioning *A type of learning where behavior is controlled by consequences. Operant and instrumental conditioning are virtually synonymous. Instrumental conditioning refers to learning in which the organism's*

behavior is shaped based on the likelihood of reinforcement.

Ophthalmic nerve *One of the three branches of the trigeminal nerve, which is the fifth cranial nerve. The ophthalmic nerve carries sensory information from the face and scalp and carries sympathetic fibers to the iris dilator muscle for pupil dilation.*

Opioid *A type of drug that acts on opioid receptors to produce morphine-like effects.*

Optic nerve *The second cranial nerve, which transmits visual from the retina of the eye to the brain.*

Organic compound *A chemical containing carbon atoms that are bound to other atoms of other elements, especially hydrogen, nitrogen, or oxygen.*

Orthostasis *Standing up.*

Orthostatic hypotension *A fall in blood pressure when a person stands up. OH has been defined by a fall in systolic blood pressure of 20 mm Hg or more or a fall in diastolic blood pressure of 10 mm or more after the person stands up for at least 3 minutes.*

Orthostatic intolerance *An inability to tolerate standing up, due to a sensation of lightheadedness or dizziness.*

Orthostatic tachycardia *An excessive increase in pulse rate when a person stands up.*

Osmolality *A measure of the amount of particles dissolved in a fluid.*

Osmopressor *Referring to an increase in blood pressure after drinking water without solute.*

Osmostat *The conceptual homeostatic comparator that keeps serum osmolality within bounds.*

Oxymetazoline *A drug that is an imidazoline like clonidine but does not readily enter the brain. Oxymetazoline is*

commonly used in over the counter nasal decongestant sprays.

-P-

Pacemaker *Something that spontaneously produces electrical impulses.*

PAF (Abbreviation for pure autonomic failure) *PAF is a disease that manifests with orthostatic hypotension.*

Palpitation *A symptom where the patient notes a forceful, rapid heartbeat or a sensation of the heart “flip-flopping” in the chest.*

Pancreas *An organ in the abdomen that secretes hormones such as insulin and digestive enzymes.*

Pancreatic polypeptide *A hormone released from the pancreas. Pancreatic polypeptide levels can provide an indirect index of vagal outflow.*

Pandysautonomia *Failure of all components of the autonomic nervous system, such as in autoimmune autonomic ganglionopathy.*

Panic disorder *A condition that features a rapid buildup of fear or anxiety that the patient cannot control.*

Parabrachial nucleus *A region at the junction of the pons and midbrain of the brainstem. The parabrachial nucleus is thought to transmit baroreceptor and other visceral afferent information from the lower brainstem to higher brain centers. The parabrachial region is part of the central autonomic network.*

Paraneoplastic *A consequence of cancer that is not due to the local presence of cancer cells.*

Parasympathetic nerve traffic *The rate of traffic in parasympathetic nerves.*

Parasympathetic nervous system (PNS) *One of the two branches of the autonomic nervous system, responsible for many “vegetative” functions such as gastrointestinal movements after a meal.*

Parasympathetic neurocirculatory failure *Failure to regulate the heart rate appropriately, such as during normal breathing or in response to the Valsalva maneuver.*

Paraventricular nucleus (PVN) *A cluster of neurons in the hypothalamus located near the third ventricle. The PVN is the source of important chemical messengers such as vasopressin, oxytocin, and corticotropin-releasing hormone. The PVN is part of the central autonomic network.*

PARK1 *A form of familial Parkinson’s disease due to A53T mutation of the gene encoding alpha-synuclein.*

PARK4 *A form of familial Parkinson’s disease due to triplication of the gene encoding alpha-synuclein.*

Parkinson disease *Same as Parkinson’s disease.*

Parkinson’s disease (PD), also called Parkinson’s disease *A disease that involves slow movements, a form of limb rigidity called “cogwheel rigidity,” and a “pill-roll” tremor that decreases with intentional movement. Other features of Parkinson’s disease include a mask-like facial expression, stooped posture, difficulty initiating or stopping movements, and small handwriting. The movement disorder in PD results from loss of dopamine-containing nerve terminals in a particular brain pathway called the nigrostriatal system. PD also involves abnormalities of the autonomic nervous system, including orthostatic hypotension.*

Parkinson’s disease with orthostatic hypotension (PD+OH) *Parkinson’s disease with a fall in blood pressure when the*

patient stands up.

Parkinsonian *Having one or more features of Parkinson's disease.*

Parkinsonian form of MSA *A form of multiple system atrophy that includes one or more features of Parkinson's disease.*

PARM *(Abbreviation for polyalanine repeat expansion mutation)*

Partial dysautonomia *(Same as Neuropathic POTS)*

Pathogenic *Capable of causing disease.*

Patient-oriented research *A format of biomedical research in which the investigator directly interacts with patients. A clinical trial is a form of patient-oriented research.*

Pavlovian conditioning *A form of association learning where two stimuli are repeatedly paired; a response that is at first elicited by the second stimulus (unconditioned stimulus) is eventually elicited by the first stimulus alone (conditioned stimulus). Pavlovian conditioning is synonymous with classical conditioning.*

PD *(Abbreviation for Parkinson's disease)*

PD+D *(Abbreviation for Parkinson's disease with dementia)*

PD+OH *(Abbreviation for Parkinson's disease with orthostatic hypotension)*

Pectus excavatum *A condition in which a person is born with the breastbone (sternum) that is indented or sunken in.*

Pentolinium *A particular type of drug that blocks chemical transmission in ganglia.*

Peptide *A short chain of amino acids.*

Percutaneous *Through the skin.*

Peri-aqueductal gray *A region of the back of the midbrain. The peri-aqueductal gray region is part of the central autonomic network.*

Percutaneous *Through the skin.*

Perfusate *A fluid used in perfusion, which is the passage of fluid through the circulatory system or lymphatic system to an organ or a tissue.*

Peripheral nervous system *The nerves and ganglia outside the central nervous system (brain and spinal cord).*

Peristalsis *Gastrointestinal movements such as after a meal that move digested material.*

PET scanning *(Abbreviation for positron emission tomographic scanning)*

PGP 9.5 *(Abbreviation for protein gene product 9.5, also known as ubiquitin C-terminal hydrolase 1, or UCHL-1) A protein expressed by nerves that is used to visualize nerve fibers in tissue samples.*

pH *The negative log of the hydrogen ion concentration in an aqueous solution.*

Phen-Fen *Two drugs, phentermine and fenfluramine, prescribed together to decrease appetite and promote weight loss.*

Phentermine *A particular drug that acts in the body as a sympathomimetic amine.*

Phenylalanine *A particular amino acid.*

Phenylalanine hydroxylase *The enzyme that converts phenylalanine to tyrosine. Phenylketonuria patients typically have low phenylalanine hydroxylase activity.*

Phenylephrine *(Brand name Neo-Synephrine™) A particular drug that constricts blood vessels by stimulating alpha-1 adrenoceptors.*

Phenylethanolamine-N-methyltransferase (PNMT) *The enzyme catalyzing the conversion of norepinephrine to epinephrine.*

Phenylketonuria (PKU) *A disease of children that results from lack of activity of a particular enzyme, phenylalanine hydroxylase, resulting in a toxic buildup of phenylalanine*

in the body.

Phenylpropanolamine (PPE) *A particular drug that acts in the body as a sympathomimetic amine.*

Pheo *(slang for pheochromocytoma)*

Pheochromocytoma *An abnormal growth that produces the catecholamines norepinephrine (noradrenaline) or epinephrine (adrenaline).*

Phosphorylation *A biochemical process that involves the addition of phosphate to an organic compound. An example of phosphorylation is the addition of phosphate to adenosine diphosphate (ADP) to form adenosine triphosphate (ATP), the main source of chemical energy in the body.*

PHOX2B *(Abbreviation for the pairedlike homeobox gene, type 2B) PHOX2B is necessary for normal development of the autonomic nervous system. Mutation of the PHOX2B gene is required to diagnose congenital central hypoventilation syndrome (CCHS).*

Phylogenetic *Referring to development and diversification of a species in the course of evolution.*

Physiological *Referring to a body function, as opposed to a body part.*

Pilomotor *Referring to the hair standing up.*

Pituitary gland *A gland located at the end of a stalk at the base of the brain that releases a variety of hormones.*

PKU *(Abbreviation for phenylketonuria)*

Plasma *The part of the blood that is left after anti-coagulated blood settles or is centrifuged (spun at a high rate in a tube).*

Plasma cell *A type of white blood cell that produces antibodies.*

Plasma epinephrine level *The concentration of epinephrine (adrenaline) in the plasma.*

Plasma metanephrines *Plasma levels of the free (unconjugated) O-methylated metabolites of norepinephrine (normetanephrine) and epinephrine (metanephrine).*

Plasma norepinephrine level *The concentration of norepinephrine (noradrenaline) in the plasma.*

Plasmapheresis *Synonymous with plasma exchange. Plasmapheresis is a process that filters the blood to remove harmful antibodies.*

Platelets *Tiny particles in the blood that when activated clump together. Platelet plugs stop bleeding from punctures in blood vessel walls.*

Pleiotropic *A situation in which one gene affects multiple, seemingly unrelated traits.*

PNMT *(Abbreviation for phenylethanolamine-N-methyltransferase) PNMT is the enzyme that catalyzes the conversion of norepinephrine to epinephrine.*

PNS *Abbreviation for parasympathetic nervous system.*

Polymorphism *A genetic change that is not as rare as a mutation but not so common as to be considered normal.*

Polysaccharide *A carbohydrate that consists of multiple sugar molecules bonded together.*

Polysomnography *A type of sleep test in which multiple parameters are monitored.*

Portal vein *A large vein coming from the spleen, stomach, pancreas, and intestines and going to the liver.*

Positive feedback loop *A situation in which a change in input about a monitored variable leads to output that makes the change in input even larger. For instance, if the room temperature in your house went up, and this led to the furnace being turned on, bringing the room temperature up even further, this would be a positive feedback loop. When there is a positive feedback loop, the level of the monitored*

variable becomes unstable.

Positron emission tomographic scanning (PET scanning) *A type of nuclear medicine scan where a positron-emitting form of a drug is injected, and particular parts of the body become radioactive, with the radioactivity detected by a special type of scanner called a PET scanner.*

Positron emitter *A chemical that releases a special type of radioactivity called positrons.*

Post-ganglionic nerves *Nerves from the ganglia that deliver signals to nerve terminals in target tissues such as the heart.*

Post-prandial hypotension *A fall in blood pressure after eating a meal.*

Postural tachycardia syndrome (POTS) *A condition where the patient has a long-term inability to tolerate standing up, along with an excessive increase in pulse rate in response to standing.*

Potassium *An important element and electrolyte found in all cells of the body.*

POTS (Abbreviation for postural tachycardia syndrome)

Post-ganglionic nerves *Nerves that originate in ganglia. Sympathetic and parasympathetic nerves are examples of post-ganglionic nerves.*

Power spectral analysis of heart rate variability *A special type of test based on changes in the heart rate over time.*

PPE (Abbreviation for phenylpropanolamine)

Prednisone *The name of a steroid drug commonly used to treat disorders involving inflammation.*

Prefrontal cortex *The part of the cerebral cortex at the front of the frontal lobe. The prefrontal cortex is thought to play key roles in a variety of complex behaviors, such as planning, executive functions, and restraint of more*

primitive emotion-related behaviors.

Pre-ganglionic nerves *Nerves of the autonomic nervous system that come from cell bodies in the spinal cord and go to the ganglia.*

Pre-symptomatic *Before symptoms occur.*

Pre-syncope *A feeling of near-fainting.*

Primitive specificity *A concept according to which each stressor has a neurochemical “signature,” with quantitatively if not qualitatively distinct central and peripheral mechanisms.*

Proamatine™ *(Brand name of midodrine)*

Procrit™ *(Brand name of erythropoietin)*

Pro-drug *A drug that works by being converted in the body to an active compound. For instance, L-DOPS is a norepinephrine pro-drug.*

Progressive Supranuclear Palsy (PSP) *A type of neurological syndrome with particular abnormalities of gaze.*

Prolactin *A protein hormone released from the anterior pituitary gland that stimulates milk production.*

Propranolol (Brand name Inderal™) *A drug that is the classical non-selective beta-adrenoceptor blocker.*

Proton *A sub-atomic particle with a positive electric charge and mass of about 1 atomic mass unit.*

Proton pump inhibitor (PPI) *A type of drug that inhibits secretion of acid in the stomach.*

Provocative test *A test designed to evoke an abnormal response of the body.*

Pseudopheo *Slang for pseudopheochromocytoma. In pseudopheochromocytoma the patient has episodes of severe high blood pressure and symptoms suggestive of a pheochromocytoma, but the patient doesn't actually have a pheochromocytoma.*

Pseudoephedrine (Sudafed™) *A particular drug that acts in the body as a sympathomimetic amine.*

Psilocybin *A psychedelic chemical found in some mushrooms.*

Ptosis *Droopy eyelid.*

Pupillometry *A test involving measuring the diameter of the pupils.*

Pupillomotor *Referring to constriction or dilation of the pupils.*

Pulmonary edema *A pathologic condition in which the lungs fill up with fluid. A common cause of pulmonary edema is heart failure.*

Puncture diabetes (piqûre) *A phenomenon described by Claude Bernard in which puncturing a particular location in the brainstem increases the glucose concentrations in the blood and urine.*

Pure autonomic failure (PAF) *A form of long-term failure of the autonomic nervous system where there is no clear evidence for degeneration of the brain. PAF manifests with orthostatic hypotension.*

Putamen *A brain structure that is part of the striatum, in the basal ganglia.*

PUT:OCC *The ratio of putamen to occipital cortex radioactivity after injection of ¹⁸F-DOPA.*

Pyridostigmine (Mestinon™) *A drug that works by blocking the enzyme that breaks down acetylcholine.*

-Q-

QSART *(Abbreviation for Quantitative Sudomotor Axon Reflex Test)*

Quantitative Sudomotor Axon Reflex Test (QSART) *A type of test of autonomic nervous system function based on the ability of drugs to evoke sweating.*

Quaternary ammonium ion *A particular chemical arrangement in which an nitrogen atom is bonded to 4 organic groups and is therefore positively charged regardless of the pH of the solution.*

Quinone *A chemical in which an even number of =O group is attached to the benzene ring of the molecule. In dopamine quinone, the adjacent –OH groups of the catechol are replaced by =O groups.*

-R-

Radiofrequency ablation *Destruction of a tissue by applying radiofrequency energy, which burns the tissue.*

Raphe nuclei *Clusters of neurons in the middle of the lower brainstem. Raphe nuclei are a major source of serotonin in the brain. They have projections to sympathetic pre-ganglionic neurons in the spinal cord.*

RAS *(Abbreviation for renin-angiotensin-aldosterone system)*

Rasagiline *A drug that inhibits monoamine oxidase-B.*

RBD *(Abbreviation for REM behavior disorder) In RBD the patients act out their dreams and thrash about in bed. Sleep studies show failure of the limbs to be flaccid during REM sleep.*

Receptors *Special proteins in the walls of cells that bind chemical messengers such as hormones.*

Reflex *An involuntary, rapid response to a stimulus, mediated by a reflex arc.*

Reflex syncope *(Synonymous with neurocardiogenic syncope, vasovagal syncope, autonomically mediated syncope, and fainting)*

REM sleep *(Abbreviation for rapid eye movement sleep) A stage of sleep involving active dreaming, in which the eyes*

move rapidly.

REM Behavior Disorder (RBD) *A condition in which the limbs fail to stay relaxed during REM sleep. The patient acts out his or her dreams.*

Renal nerve ablation *A technique to treat hypertension by destroying sympathetic nerves of the kidneys.*

Renin *An enzyme of the renin-angiotensin-aldosterone system that converts angiotensinogen to angiotensin I.*

Renin-Angiotensin-Aldosterone system *A system that plays an important role in maintaining the correct amount of blood volume and sodium in the body.*

Reserpine *A drug that blocks the vesicular monoamine transporter and thereby depletes stores of monoamines such as catecholamines and serotonin.*

Respiratory sinus arrhythmia *The normal changes in pulse rate that occur with breathing.*

Reticular Activating System (RAS) *A diffuse network of nerve pathways in the brainstem connecting widely with the spinal cord, cerebral cortex, and cerebellum, thought to mediate the level of consciousness.*

Retrotrapezoid nucleus (RTN) *A brainstem region that plays an important role in regulation of respiration.*

Review of Systems (ROS) *An inventory of symptoms based on querying about functions of different body systems.*

Riley-Day syndrome *An eponym for Familial Dysautonomia, or FD.*

Ritalin™ *(Brand name of methylphenidate) A particular drug that resembles amphetamine.*

Rituximab *An anti-autoimmune drug that destroys antibody-producing B cells.*

RNA *(Abbreviation for ribonucleic acid) RNA is vital for producing proteins based on genetic instructions in the*

DNA.

Ross's syndrome A condition in which there is Adie's pupil, loss deep tendon reflexes, and altered sweating.

Rostral ventrolateral medulla (RVLM) The outer, upper part of the medulla of the brainstem. The RVLM is a major source of nerve fibers that descend in the spinal cord to the sympathetic pre-ganglionic neurons.

RVLM (Abbreviation for rostral ventrolateral medulla)

Ryanodine receptor A member of a class of receptors that act as intra-cellular calcium channels.

-S-

S-adenosyl methionine (SAdMe) A molecule that is a source of methyl groups in some biochemical reactions. SAdMe is the methyl donor for the O-methylation of catecholamines by catechol-O-methyltransferase (COMT).

Sacral Referring to the sacrum, the triangular bone in the lower back between the two hip bones of the pelvis.

Sacral nerve A spinal nerve coming from the lower-most portion of the spinal cord.

SAI (Abbreviation for sympathoadrenal imbalance)

Saline A solution of salt in water.

Salivation Formation of spit.

Salivary glands Glands in the head that produce saliva.

SAS (Abbreviation for sympathetic adrenergic system) The SAS is the part of the sympathetic nervous system for which adrenaline is the main chemical messenger. The SAS is also called the adrenomedullary hormonal system.

SCS (Abbreviation for sympathetic cholinergic system) The SCS is the part of the sympathetic nervous system for which acetylcholine is the main chemical messenger. The SCS is

especially involved in sweating.

Scientific Integrative Medicine *A conceptual framework for linking systems biology with integrative physiology in order to understand disease mechanisms. The concepts include (i) negative feedback regulation; (ii) homeostats; (iii) multiple effectors; (iv) effector sharing; (v) stress; (vi) distress; (vii) allostasis; and (viii) allostatic load.*

Scotoma *A blind spot in the visual field, surrounded by an area of more normal vision. Scintillating scotoma is also called visual migraine.*

SEC *(Abbreviation for skin electrical conductance)*

Second messenger *A molecule that relay signals received at receptors on the cell surface to target molecules in the cytoplasm or nucleus.*

Secretomotor *Referring to secretion from a gland, such as salivation, tear production, and sweating.*

Segawa's disease *Synonymous with DOPA-responsive dystonia.*

Selective Serotonin Reuptake Inhibitor (SSRI) *A type of drug that inhibits neuronal uptake of serotonin.*

Selegiline *A drug that inhibits monoamine oxidase-B.*

Sensitization *The process by which repetition of a stimulus amplifies the physiological or emotional response.*

Sepiapterin reductase *An enzyme in the synthetic cascade leading to tetrahydrobiopterin.*

Sepsis *A life-threatening condition from generalized infection in the body.*

Serotonin *(Synonymous with 5-hydroxytryptamine, 5-HT) A particular chemical messenger in a family called monoamines. Catecholamines are also monoamines.*

Short-Lasting Unilateral Neuralgiform Headache with Conjunctival Injection and Tearing *(Abbreviation:*

SUNCT) *A syndrome involving episodic painful headache with conjunctival injection and tearing.*

Shy-Drager syndrome *Eponym for multiple system atrophy with orthostatic hypotension.*

Sign *Something a doctor can observe or measure that provides objective evidence of a disease.*

Sinemet™ *Brand name of levodopa combined with carbidopa.*

Sinus node *The pacemaker area of the heart that normally generates the electrical impulses resulting in a coordinated heartbeat.*

Sinus node ablation *Destruction of the sinus node in the heart, usually as a treatment for excessively rapid heart rate.*

Sjogren's syndrome *An autoimmune condition characterized by dry mouth and dry eyes.*

Skin electrical conductance (SEC) *A measure of the ability of the skin to conduct electricity. Because of electrolytes in sweat, when a person sweats SEC increases.*

Skin sympathetic test (SST) *A type of test of the sympathetic nervous system based on the ability of various drugs or environmental manipulations to increase secretion of sweat.*

Sodium *An important chemical element found in all body fluids.*

Somatic nervous system *The somatic nervous system is the main way the body deals with the "outside world," by way of its main target organ, skeletal muscle.*

Smooth muscle cells *The type of muscle cells in the heart and in blood vessel walls.*

SNS (Abbreviation for sympathetic noradrenergic system) *The SNS is the part of the sympathetic nervous system for which norepinephrine is the chemical messenger. The SNS is especially important for regulation of the heart and blood vessels.*

Somatization *Recurrent, multiple medical symptoms without a discernible organic cause.*

Somatostatin (Octreotide™) *A type of drug that when injected can raise the blood pressure in patients with autonomic failure.*

Sphincter *A circular smooth muscle that normally maintains constriction of a body passage.*

Sphingolipid *Any of a class of compounds that are fatty acid derivatives of sphingosine. Sphingolipids are components of nerve cell membranes.*

Spillover *The estimated rate of entry of an endogenous compound into the bloodstream. Cardiac norepinephrine spillover is the rate of entry of norepinephrine into the venous drainage of the heart.*

Spinal nerve *A nerve that carries motor, sensory, and autonomic signals between the spinal cord and the body. There are 31 pairs of spinal nerves, each one exiting from the side of the vertebral column.*

SSRI (Abbreviation for selective serotonin reuptake inhibitor) *SSRIs block one of the main ways of inactivating and recycling the chemical messenger, serotonin. SSRIs are used to treat depression, anxiety, and other psychiatric or emotional problems.*

SST (Abbreviation for skin sympathetic test)

Stereoisomer *A mirror image structure of a chemical.*

Strain gauge *A testing device that sensitively measures stretch.*

Stress *A condition in which the brain senses a challenge to physical or mental stability that leads to altered activities of body systems to meet that challenge.*

Stress cardiopathy *Heart dysfunction or failure due to distress.*

Stressor *According to Selye, that which results in a state of stress.*

Striatonigral degeneration *A form of nervous system disease where the patient seems to have Parkinson's disease but does not respond well to treatment with levodopa.*

Striata *Plural of striatum.*

Striatal *Referring to the striatum in the basal ganglia of the brain.*

Striatum (Same as corpus striatum) *A structure in the basal ganglia of the brain that includes the caudate and putamen.*

Stridor *A harsh inspiratory crowing noise, caused by obstruction or dysregulation of the vocal cords.*

Stroke Index *The cardiac stroke volume adjusted for body surface area.*

Stroke volume *The amount of blood pumped by the heart in one heartbeat.*

Subcortical *Below the level of the cerebral cortex. The brainstem is subcortical.*

Substantia nigra *A black pigmented region of the midbrain that is the major source of dopamine in the brain.*

Sudafed™ *(Brand name of pseudoephedrine)*

Sudomotor *Referring to the ability to secrete sweat.*

Sulci *Grooves in the surface of the brain.*

SUNCT *(Abbreviation for Short-Lasting Unilateral Neuralgiform Headache with Conjunctival Injection and Tearing)*

Superior cervical ganglion *A sympathetic ganglion in the upper neck.*

Sympathectomy *Surgical removal or destruction of ganglia, which results in absence of traffic in sympathetic nerves.*

Sympathetic adrenergic system *A part of the sympathetic nervous system for which adrenaline is the main chemical messenger. Synonymous with adrenomedullary hormonal*

system.

Sympathetic cholinergic system (SCS) *A part of the sympathetic nervous system for which acetylcholine is the chemical messenger. This part is especially important for regulation of sweating.*

Sympathetic innervation *The supply of sympathetic nerves in a tissue or organ.*

Sympathetic nerve terminals *Endings of sympathetic nerves, from which the chemical messenger, norepinephrine (noradrenaline) is released.*

Sympathetic nerve traffic *Nerve impulses in sympathetic nerve fibers.*

Sympathetic nerves *Nerves of the sympathetic nervous system.*

Sympathetic nervous system *One of the branches of the autonomic nervous system, responsible for many “automatic” functions such as constriction of blood vessels when a person stands up.*

Sympathetic neurocirculatory failure *Failure of regulation of the heart and blood vessels by the sympathetic nervous system.*

Sympathetic noradrenergic system (SNS) *A part of the sympathetic nervous system for which norepinephrine is the chemical messenger. This part is especially important for regulation of the heart and blood vessels.*

Sympathetic neuroimaging *Visualization of the sympathetic nerves in the body.*

Sympathetic vasoconstrictor tone *The status of constriction of blood vessels as a result of traffic in sympathetic nerves.*

Sympathetically-mediated hypertension *High blood pressure due to increased sympathetic noradrenergic system activity.*

Sympathin *A word used by Walter B. Cannon to refer to a*

chemical produced by stimulating sympathetic nerves and diffusing into circulation.

Sympathoadrenal imbalance (SAI) *A situation in which plasma epinephrine levels increase to a greater extent than do plasma norepinephrine levels. SAI is a typical finding before or at the time of fainting.*

Sympathoadrenal system (also called the sympathetic adrenergic system, sympathico-adrenal system, or sympathoadrenomedullary system) *A name for the sympathetic nervous system and adrenomedullary hormonal system acting as a unit.*

Sympathomimetic amine *A type of drug that acts in the body like stimulation of the sympathetic nervous system.*

Sympathotonic orthostatic intolerance *Inability to tolerate standing up that is associated with excessive activity of the sympathetic nervous system.*

Symptom *A complaint about something abnormal a person notices that provides subjective evidence of a disease.*

Syncope *Sudden loss of consciousness due to decreased flow of blood to the brain. In syncope the sudden loss of consciousness is associated with loss of muscle tone and the regaining of consciousness within seconds to minutes.*

Syndrome *A set of symptoms that occur together.*

Synuclein *A particular protein found especially in nervous tissue.*

Synucleinopathies *A family of diseases characterized by deposition of the protein, alpha-synuclein, in the cytoplasm of affected cells. Parkinson's disease is an example of a synucleinopathy.*

Systems biology *Systems biology has been defined variously. One definition is the study of dynamic interactions within biological networks.*

Systolic blood pressure *The peak blood pressure while the heart is pumping out blood.*

-T-

T cell (also called T lymphocyte) *A type of lymphocyte white blood cell that plays a central role in cell-mediated (as opposed to antibody-mediated) immunity.*

Tachycardia *Excessively fast heart rate.*

Takotsubo cardiopathy *A form of stress-related acute heart failure that is most common in post-menopausal women and probably due to high catecholamine levels.*

Tardive dyskinesia *A complication of dopamine receptor antagonists that involves involuntary movements of the jaw or tongue.*

Teleological *Explaining actions by their results. Teleology is a reason or explanation for something in terms of its purpose or goal.*

Temperomandibular joint disorder (TMJ) *A condition involving pain and decreased movement of the jaw joint.*

Tensilon™ *Brand name for edrophonium. Tensilon rapidly, temporarily blocks acetylcholinesterase. The drug is used to help diagnose myasthenia gravis.*

Tetrabenazine (TBZ) *A drug that blocks the type 2 vesicular monoamine transporter.*

Tetrahydrobiopterin (BH4) *A key co-factor for some enzymes, including tyrosine hydroxylase.*

TH (Abbreviation for tyrosine hydroxylase) *TH is the rate-limiting enzyme in catecholamine biosynthesis.*

Thermoregulatory sweat test (TST) *A test based on the ability of the patient to produce sweat in response to an increase in environmental temperature.*

Thermostat *The conceptual homeostatic comparator that keeps core temperature stable.*

Thoracolumbar spinal cord *The mid-portion of the spinal cord from which sympathetic nerves emerge.*

Thyroid *Paired glands in the neck that produce the hormone, thyroxine.*

Tilt table testing *A test where the patient is tilted on a platform, to assess the ability of the patient to tolerate and respond appropriately to standing up.*

Tinnitus *A sense of high-pitched ringing in the ears.*

Tissue *A group of cells within an organ that carry out specific functions.*

TMJ *(Abbreviation for temporomandibular joint)*

TNF- α *(Abbreviation for tumor necrosis factor-alpha) TNF- α is a type of cytokine.*

Tomography (or tomographic scan) *A type of scan where a part of the body is visualized in slices.*

Total peripheral resistance (TPR) *The total amount of resistance to blood flow in the body.*

Total peripheral vascular resistance *Synonymous with total peripheral resistance, the total amount of resistance to blood flow in the body.*

TPR *(Abbreviation for total peripheral resistance) TPR is the total amount of resistance to blood flow in the body.*

Transcription factor *A type of protein that affects the process of converting, or transcribing, DNA into RNA*

Transthyretin (TTR) *A protein related to amyloidosis. Mutation of the TTR gene results in accumulation of the abnormal protein in a variety of organs and tissues.*

Tremor *Involuntary shaking.*

Tricyclic *A particular chemical structure of a drug. Tricyclics include some commonly used anti-depressants.*

Trigeminal nerve *The fifth cranial nerve, which supplies the face.*

Triglycerides *Particular chemicals derived from glycerol and fatty acids. Triglycerides are the main constituents of body fat in humans.*

Trimethaphan (Arfonad™) *A particular type of drug that blocks chemical transmission in ganglia.*

Trimethaphan infusion test *A test where trimethaphan is given by vein, to assess the effects on blood pressure.*

Trophic *Causing a growth effect.*

Tropic *Causing a change in, or affecting.*

Tryptase *An enzyme found in granules of mast cells that has been used as a marker for mast cell activation.*

TST (Abbreviation for thermoregulatory sweat test)

Tuberoinfundibular (or tuberohypophyseal) system *A neurochemical system in the brain in which dopamine is delivered from the hypothalamus to the pituitary gland.*

Tyramine (TYR) *A sympathomimetic amine found in foodstuffs such as hard cheese and red wine.*

Tyramine infusion test *A particular autonomic function test in which tyramine is given IV and the physiological or neurochemical effects are measured.*

Tyrosinase *An enzyme involved in the production of melanin from tyrosine.*

Tyrosine *An essential amino acid. Tyrosine is converted to DOPA by tyrosine hydroxylase.*

Tyrosine hydroxylase (TH) *An important enzyme required for production of the catecholamines dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline) in the body.*

-U-

Unmyelinated Same as non-myelinated. Lacking a myelin sheath. Post-ganglionic autonomic neurons are unmyelinated.

UPSIT (Abbreviation for the University of Pennsylvania Smell Identification Test)

Uptake-1 Uptake of norepinephrine and related chemicals by way of the cell membrane norepinephrine transporter, such as uptake into sympathetic nerves.

Uptake-2 Uptake of norepinephrine and related chemicals by way of a transporter on non-neuronal cells such as myocardial cells.

Urecholine™ A brand of bethanechol, a drug that stimulates muscarinic cholinergic receptors.

-V-

VACHT (Abbreviation for vesicular acetylcholine transporter)

The VACHT is a protein in the walls of storage vesicles in cholinergic neurons that transports acetylcholine into the vesicles.

Vagal parasympathetic outflow Traffic in the vagus nerve, a main nerve of the parasympathetic nervous system.

Vagus nerve The tenth cranial nerve. The vagus is the main nerve of the parasympathetic nervous system.

Vagusstoff A term used by Otto Loewi referring to the chemical messenger released from the stimulated vagus nerve. Loewi identified the Vagusstoff as acetylcholine, and for this discovery he received a Nobel Prize.

Valsalva maneuver A maneuver where a person blows against a resistance or strains against a closed glottis, resulting in an increase in pressure in the chest and a decrease in the

- venous return to and the ejection of blood by the heart.*
- Vanillylmandelic acid (VMA)** *A major end-product of norepinephrine metabolism.*
- Vascular resistance** *Resistance to blood flow.*
- Vasoactive intestinal peptide (VIP)** *A small protein produced in the gut, brain, and other organs and used to identify sympathetic cholinergic neurons.*
- Vasoconstriction** *Tightening of blood vessel walls.*
- Vasodepressor syncope** *Same as Autonomically Mediated Syncope, Reflex Syncope, Neurocardiogenic syncope, and Neurally Mediated Syncope.*
- Vasodilation** *Widening of blood vessels due to relaxation of smooth muscle cells within the vessel walls.*
- Vasomotor** *Referring to constriction of blood vessels.*
- Vasopressin** *Same as antidiuretic hormone, arginine vasopressin, AVP. Vasopressin is a hormone released from the pituitary gland at the base of the brain that stimulates retention of water by the kidneys and increases blood pressure by constricting blood vessels.*
- Vein** *A type of blood vessel that carries blood toward the heart.*
- Venlafaxine (Effexor™)** *A drug that acts as a combined serotonin and norepinephrine reuptake inhibitor.*
- Venous return** *Return of blood to the heart by the veins.*
- Ventricles** *The main pumping chambers of the heart. The right ventricle contains blood pumped by the heart to the lungs. The left ventricle contains blood pumped by the heart to the rest of the body. The left ventricular myocardium is the main pumping muscle of the heart.*
- Ventricular arrhythmia** *An abnormal rhythm of the heart ventricles.*
- Ventriculogram** *A radiologic procedure in which a radio-opaque dye is injected to reveal the ventricular cavity in*

the heart.

Vertebrae *Bones of the backbone. Each vertebra has sites for articulation and muscle attachment and a hole through which the spinal cord passes.*

Vertebral column *The backbone, consisting of 33 vertebrae (7 cervical, 12 thoracic, 5 lumbar, 5 fused sacral, 4 frequently fused coccygeal).*

Vesicles *Tiny bubble-like structures inside nerves and endocrine cells. Vesicles store chemical messengers such as norepinephrine.*

Vesicular acetylcholine transporter (VACHT) *A particular type of protein in the walls of storage vesicles that transports acetylcholine into the vesicles.*

Vesicular monoamine transporter (VMAT) *A particular type of protein in the walls of storage vesicles that transports chemicals such dopamine into the vesicles.*

Viscera *A general term referring to the internal organs in the cavities of the body. Viscera often means abdominal cavity contents—the gastrointestinal tract, pancreas, spleen, liver, and kidneys.*

Vitamin *An organic compound that an organism requires in limited amounts and is obtained through the diet.*

VMA *(Abbreviation for vanillylmandelic acid) VMA is a major breakdown product of norepinephrine.*

VMAT (Abbreviation for the vesicular monoamine transporter) *VMATs are proteins in the walls of vesicles in monoaminergic neurons that transport monoamines from the cytoplasm into the vesicles.*

VMAT2 (Abbreviation for the type 2 vesicular monoamine transporter) *VMAT2 is important for the storage of catecholamines in vesicles in sympathetic nerves and in the brain.*

Voltage-gated *A characteristic of membrane ion channels that are activated by changes in the electrical membrane potential nearby them.*

Volustat *The conceptual homeostatic comparator that keeps blood volume within bounds.*

-X-

X-Chromosome *One of the two sex-determining chromosomes.*

X-linked *A mode of inheritance in which the genetic abnormality is on the X chromosome.*

-Y-

Yohimbe bark *A naturally occurring form of yohimbine that is available as an over-the-counter herbal remedy.*

Yohimbine *A drug that blocks alpha-2 adrenoceptors in the brain, in blood vessel walls, and on sympathetic nerve terminals.*

Yohimbine challenge test *A type of autonomic function test in which yohimbine is administered and blood pressure and plasma levels of norepinephrine or other neurochemicals are measured.*